



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification ⁶ : C07C 311/15, 311/20, 311/21, 311/37, 311/25, C07D 333/34, 213/38, 233/54, 307/52, 333/20, A61K 31/18, 31/44, 31/34, 31/38, 31/415 | | A1 | (11) International Publication Number: WO 99/55667 (43) International Publication Date: 4 November 1999 (04.11.99) | | |
| (21) International Application Number: PCT/US99/07971 | | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). | | | |
| (22) International Filing Date: 12 April 1999 (12.04.99) | | Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> | | | |
| (30) Priority Data: 60/083,415 29 April 1998 (29.04.98) US Not furnished 12 April 1999 (12.04.99) US | | | | | |
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| (54) Title: N-SUBSTITUTED AMINOTETRALINS AS LIGANDS FOR THE NEUROPEPTIDE Y Y5 RECEPTOR USEFUL IN THE TREATMENT OF OBESITY AND OTHER DISORDERS | | | | | |
| <p style="text-align: center;"> $\begin{array}{c} \text{R}_2 \\ \\ \text{B}_2 - \text{C}(\text{Y})_m - \text{C}(\text{H}) - \text{N} - \text{L} - \text{N}(\text{H}) - \text{S}(\text{O})\text{R}_3 \\ \\ \text{B}_1 \end{array} \quad (1)$ </p> | | | | | |
| (57) Abstract | | | | | |
| <p>β-Aminotetralin derivatives of formula (1): which are ligands for the neuropeptide Y Y5 (NPY5) receptor, methods of preparation and pharmaceutical compositions containing a β-aminotetralin derivative as the active ingredient are described. The β-aminotetralins are useful in the treatment of disorders and diseases associated with NPY receptor subtype Y5.</p> | | | | | |

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**N-SUBSTITUTED AMINOTETRALINS AS LIGANDS
FOR THE NEUROPEPTIDE Y Y5 RECEPTOR
USEFUL IN THE TREATMENT OF OBESITY AND OTHER DISORDERS**

5 This application is based on provisional application Ser. No. 60/083,415, filed April 29, 1998.

FIELD OF THE INVENTION

10 This invention relates to a series of β -aminotetralin derivatives, pharmaceutical compositions containing them and intermediates used in their preparation. The compounds of the invention are ligands for the neuropeptide Y Y5 (NPY5) receptor, a receptor which is associated with a number of central nervous system disorders and affective conditions. In addition, many of the 15 compounds of the invention reduce food consumption in a rodent model of feeding.

BACKGROUND OF THE INVENTION

20 Regulation and function of the mammalian central nervous system is governed by a series of interdependent receptors, neurons, neurotransmitters, and proteins. The neurons play a vital role in this system, for when externally or internally stimulated, they react by releasing neurotransmitters that bind to specific proteins. Common examples of endogenous small molecule 25 neurotransmitters such as acetylcholine, adrenaline, norepinephrine, dopamine, serotonin, glutamate, and gamma-aminobutyric acid are well known, as are the specific receptors that recognize these compounds as ligands ("The Biochemical Basis of Neuropharmacology", Sixth Edition, Cooper, J. R.; Bloom, F. E.; Roth, R. H. Eds., Oxford University Press, New 30 York, NY 1991).

In addition to the endogenous small molecule neurotransmitters, there is increasing evidence that neuropeptides play an integral role in neuronal

operations. Neuropeptides are now believed to be co-localized with perhaps more than one-half of the 100 billion neurons of the human central nervous system. In addition to humans, neuropeptides have been discovered in a number of animal species. In some instances the composition of these 5 peptides is remarkably homogenous among species. This finding suggests that the function of neuropeptides is vital and has been impervious to evolutionary changes. Furthermore, neuropeptides, unlike small molecule neurotransmitters, are typically synthesized by the neuronal ribosome. In some cases, the active neuropeptides are produced as part of a larger protein 10 which is enzymatically processed to yield the active substance. Based upon these differences, compared to small molecule neurotransmitters, neuropeptide-based strategies may offer novel therapies for CNS diseases and disorders. Specifically, agents that affect the binding of neuropeptides to their respective receptors or ameliorate responses that are mediated by 15 neuropeptides are potential therapies for diseases associated with neuropeptides.

There are a number of afflictions that are associated with the complex interdependent system of receptors and ligands within the central nervous 20 system; these include neurodegenerative diseases, affective disorders such as anxiety, depression, pain and schizophrenia, and affective conditions that include a metabolic component, namely obesity. Such conditions, disorders and diseases have been treated with small molecules and peptides which modulate neuronal responses to endogenous neurotransmitters.

25

One example of the class of neuropeptides is neuropeptide Y (NPY). NPY was first isolated from porcine brain (Tatemoto, K. et al. *Nature* 1982, 296, 659) and was shown to be structurally similar to other members of the pancreatic polypeptide (PP) family such as peptide YY, which is primarily 30 synthesized by endocrine cells in the gut, and pancreatic polypeptide, which is synthesized by the pancreas. Neuropeptide Y is a single peptide protein that consists of thirty-six amino acids containing an amidated C-terminus. Like other members of the pancreatic polypeptide family, NPY has a distinctive

conformation that consists of an N-terminal polyproline helical region and an amphiphilic α -helix joined by a characteristic PP-fold (Vladimir, S. et. Al. *Biochemistry* 1990, 20, 4509). Furthermore, NPY sequences from a number of animal species have been elucidated and all show a high degree of amino acid 5 homology to the human protein (>94% in rat, dog, rabbit, pig, cow, sheep) (see Larhammar, D. in "The Biology of Neuropeptide Y and Related Peptides", Colmers, W. F. and Wahlestedt, C. Eds., Humana Press, Totowa, NJ 1993).

Endogenous receptor proteins that bind NPY and related peptides as 10 ligands have been identified and distinguished, and several such proteins have been cloned and expressed. Six different receptor subtypes [Y1, Y2, Y3, Y4(PP), Y5, Y6 (formerly designated as a Y5 receptor)] are recognized today based upon binding profile, pharmacology and / or composition if identity is known (Wahlestedt, C. et. al. *Ann. NY Acad. Sci.* 1990, 611, 7; Larhammar, D. 15 et. al. *J. Biol. Chem.* 1992, 267, 10935; Wahlestedt, C. et. al. *Regul. Pept.* 1986, 13, 307; Fuhlendorff, J. U. et. al. *Proc. Natl. Acad. Sci. USA* 1990, 87, 182; Grundemar, L. et. al. *J. Pharmacol. Exp. Ther.* 1991, 258, 633; Laburthe, M. et. al. *Endocrinology* 1986, 118, 1910; Castan, I. et. al. *Endocrinology* 1992, 131, 1970; Gerald, C. et. al. *Nature* 1996, 382, 168; Weinberg, D. H. et. al. 20 *Journal of Biological Chemistry* 1996, 271, 16435; Gehlert, D. et. al. *Current Pharmaceutical Design* 1995, 1, 295; Lundberg, J. M. et. al. *Trends in Pharmaceutical Sciences* 1996, 17, 301). Most and perhaps all NPY receptor proteins belong to the family of so-called G-protein coupled receptors (GPCRs). The neuropeptide Y5 receptor, a putative GPCR, is negatively 25 coupled to cellular cyclic adenosine monophosphate (cAMP) levels via the action of adenylate cyclase (Gerald, C. et. al. *Nature* 1996, 382, 168; Gerald, C. et. al. PCT WO 96/16542). For example, NPY inhibits forskolin-stimulated cAMP production / levels in a neuroblastoma cell line. A Y5 ligand that mimics NPY in this fashion is an agonist whereas one that competitively reverses the 30 NPY inhibition of forskolin-stimulated cAMP production is an antagonist.

Neuropeptide Y itself is the archetypal substrate for the NPY receptors and its binding can elicit a variety of pharmacological and biological effects in

vitro and *in vivo*. When administered to the brain of live animals (intracerebroventricularly (icv) or into the amygdala), NPY produces anxiolytic effects in established animal models of anxiety such as the elevated plus-maze, Vogel punished drinking and Geller-Seifter's bar-pressing conflict 5 paradigms (Heilig, M. et. al. *Psychopharmacology* 1989, 98, 524; Heilig, M. et. al. *Reg. Peptides* 1992, 41, 61; Heilig, M. et. al. *Neuropsycho-pharmacology* 1993, 8, 357). Thus compounds that mimic NPY are postulated to be useful for the treatment of anxiolytic disorders.

10 The immunoreactivity of neuropeptide Y is notably decreased in the cerebrospinal fluid of patients with major depression and those of suicide victims (Widdowson, P. S. et. al. *Journal of Neurochemistry* 1992, 59, 73), and rats treated with tricyclic antidepressants display significant increases of NPY relative to a control group (Heilig, M. et. al. *European Journal of Pharmacology* 15 1988, 147, 465). These findings suggest that an inadequate NPY response may play a role in some depressive illnesses, and that compounds that regulate the NPY-ergic system may be useful for the treatment of depression.

20 Neuropeptide Y improves memory and performance scores in animal models of learning (Flood, J. F. et. al. *Brain Research* 1987, 421, 280) and therefore may serve as a cognition enhancer for the treatment of neurodegenerative diseases such as Alzheimer's Disease (AD) as well as AIDS-related and senile dementia.

25 Elevated plasma levels of NPY are present in animals and humans experiencing episodes of high sympathetic nerve activity such as surgery, newborn delivery and hemorrhage (Morris, M. J. et. al. *Journal of Autonomic Nervous System* 1986, 17, 143). Thus chemical substances that alter the NPY-ergic system may be useful for alleviating the condition of stress.

30 Neuropeptide Y also mediates endocrine functions such as the release of luteinizing hormone (LH) in rodents (Kalra, S. P. et. al. *Frontiers in Neuroendocrinology* 1992, 13, 1). Since LH is vital for mammalian ovulation,

a compound that mimics the action of NPY could be useful for the treatment of infertility, particularly in women with so-called luteal phase defects.

Neuropeptide Y is a powerful stimulant of food intake; as little as one-billionth of a gram, when injected directly into the CNS, causes sated rats to overeat (Clark, J. T. et. al. *Endocrinology* **1984**, *115*, 427; Levine, A. S. et. al. *Peptides* **1984**, *5*, 1025; Stanley, B. G. et. al. *Life Sci.* **1984**, *35*, 2635; Stanley, B. G. et. al. *Proc. Nat. Acad. Sci. USA* **1985**, *82*, 3940). Thus NPY is orexigenic in rodents but not anxiogenic when given intracerebroventricularly and so antagonism of neuropeptide receptors may be useful for the treatment of eating disorders such as obesity, anorexia nervosa and bulimia nervosa.

In recent years, a variety of potent, structurally distinct small molecule Y1 antagonists has been discovered and developed (Hipskind, P. A. et. al. *Annu. Rep. Med. Chem.* **1996**, *31*, 1-10; Rudolf, K. et. al. *Eur. J. Pharmacol.* **1994**, *271*, R11; Serradeil-Le Gal, C. et. al. *FEBS Lett.* **1995**, *362*, 192; Wright, J. et. al. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1809; Poindexter, G. S. et. al. United States Patent 5,668,151; Peterson, J. M. et. al. WO9614307 (1996)). However, despite claims of activity in rodent models of feeding, it is unclear if inhibition of a feeding response can be attributed to antagonism of the Y1 receptor.

Several landmark studies strongly suggest that an "atypical Y1" receptor and / or the Y5 receptor, rather than the classic Y1 receptor, is responsible for invoking NPY-stimulated food consumption in animals. It has been shown that the NPY fragment NPY2-36 is a potent inducer of feeding despite poor binding at the classic Y1 receptor (Stanley, B. G. et. al. *Peptides* **1992**, *13*, 581). Conversely, a potent and selective Y1 agonist has been reported to be inactive at stimulating feeding in animals (Kirby, D. A. et. al. *J. Med. Chem.* **1995**, *38*, 4579). More pertinent to the invention described herein, [D-Trp³²]NPY, a selective Y5 receptor activator has been reported to stimulate food intake when injected into the hypothalamus of rats (Gerald, C. et. al. *Nature* **1996**, *382*, 168). Since [D-Trp³²]NPY appears to be a full agonist of the Y5 receptor

with no appreciable Y1 activity, the Y5 receptor is hypothesized to be responsible for the feeding response. Accordingly compounds that antagonize the Y5 receptor should be effective in inhibiting food intake, particularly that stimulated by NPY.

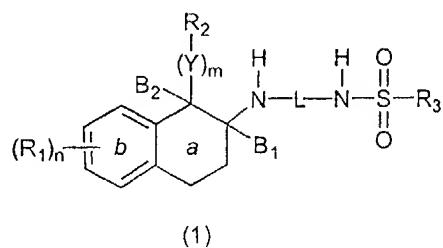
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Also pertinent to the invention described herein, are disclosures of arylsulfonamides that act as Y5 antagonists. In PCT WO 97/19682, aryl sulfonamides and sulfamides derived from arylalkylamines are described as Y5 antagonists and are reported to reduce food consumption in animals. In 10 PCT WO 97/20820, PCT WO 97/20822 and PCT WO 97/20823, sulfonamides containing heterocyclic systems such as quinazolin-2,4-diazirines, are likewise claimed as Y5 antagonists and reported to reduce feeding. There is no disclosure in any of these publications of an α -substituted β -aminotetralin. The 15 N-substituted aminotetralins described in this application are novel molecular entities that may have binding motifs that are different than these and other Y5 ligands that have been disclosed in patent applications or publications, and yet bind to a similar region of the Y5 receptor.

SUMMARY OF THE INVENTION

20

The present invention is related to compounds of formula 1



25 R_1 is independently selected from the group consisting of hydrogen; hydroxy; halo; C_{1-8} alkyl; substituted C_{1-8} alkyl wherein the substituent is selected from halo, such as chloro, bromo, and fluoro; C_{1-8} alkoxy; substituted C_{1-8} alkoxy wherein the substituent is selected from halo, such as chloro, bromo, fluoro and iodo; trifluoroalkyl; C_{1-8} alkylthio and

substituted C_{1-8} alkylthio wherein the substituent is selected from halo, such as chloro, bromo, fluoro and iodo, trifluoroalkyl and C_{1-8} alkoxy; C_{3-6} cycloalkyl; C_{3-8} cycloalkoxy; nitro; amino; C_{1-6} alkylamino; C_{1-6} dialkylamino; C_{4-8} cycloalkylamino; cyano; carboxy; C_{1-5} alkoxycarbonyl; 5 C_{1-5} alkylcarbonyloxy; formyl; carbamoyl; phenyl; substituted phenyl wherein the substituent is selected from halo, hydroxyl, nitro, amino and cyano;

- n is 0-2
- 10 B_2 is selected from the group consisting of hydrogen; C_{1-5} alkyl; substituted C_{1-5} alkyl wherein the substituent is halogen;
- 15 B_2 may have either a *cis*- or *trans*- stereochemical orientation with respect to B_1 ; both enantiomers of each diastereomeric set are part of the present invention;
- Y is methylene
- 20 m 0-3
- R_2 is selected from the group consisting of hydrogen; hydroxy; C_{1-6} alkyl; C_{1-6} alkenyl; halo, such as fluoro and chloro; C_{3-7} cycloalkyl; phenyl; substituted phenyl wherein the substituent is selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, trifluoro C_{1-6} alkyl, cyano, nitro, amino, C_{1-6} alkylamino, and C_{1-6} dialkylamino; naphthyl; phenoxy; substituted phenoxy wherein the substituent is selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, trifluoro C_{1-6} alkyl, cyano and nitro; phenylthio and substituted phenylthio wherein the substituent is selected from halo, C_{1-6} alkyl, nitro and amino; a heteroaryl group such as pyridyl, pyrimidyl, furyl, thienyl, and imidazolyl; 25 substituted heteroaryl wherein the substituent is selected from C_{1-6} alkyl and halo; and heterocycloalkyl such as pyrrolidino or piperidino;
- 30

- B₁ is selected from the group consisting of hydrogen; C₁₋₅alkyl; substituted C₁₋₅alkyl wherein the substituent is halo;
- 5 B₁ may have either a *cis*- or *trans*- stereochemical orientation with respect to B₂; both enantiomers of each diastereomeric set are part of this invention.
- L is selected from the group consisting of
C₁₋₈alkylene; C₂₋₁₀alkenylene; C₂₋₁₀alkynylene;
10 C₁₋₄alkyleneC₃₋₇cycloalkylene; C₁₋₄alkyleneC₃₋₇cycloalkylC₁₋₄alkylene;
C₂₋₄alkenyleneC₃₋₇cycloalkylC₂₋₄alkenylene;
C₂₋₄alkynyleneC₃₋₇cycloalkylC₂₋₄alkynylene; C₁₋₄alkylenearylC₁₋₄alkylene;
and
C₂₋₄alkenylenearylC₂₋₄alkenylene;
- 15 R₃ is selected from C₁₋₈alkyl; substituted C₁₋₈alkyl wherein the substituent is selected from alkoxy and halo; cycloalkyl; substituted cycloalkyl wherein the substituent is selected from alkoxy and halo; phenyl; substituted phenyl wherein the substituent is selected from C₁₋₈alkyl, halo, nitro, amino, alkylamino, alkylsulfonyl, alkoxy and cyano; naphthyl; substituted naphthyl wherein the substituent is selected from halo, nitro, amino and cyano; heteroaryl wherein the heteroaryl group is selected from pyridyl, pyrimidyl, furyl, thieryl and imidazolyl; and substituted heteroaryl wherein the substituent is selected from halo, nitro, amino and cyano;
- 20
25 and enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

As used herein unless otherwise noted the terms "alkyl" and "alkoxy"
30 whether used alone or as part of a substituent group, include straight and branched chains having 1-8 carbon atoms. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, *t*-butyl, pentyl, 2-methyl-3-butyl, 1-methylbutyl, 2-methylbutyl, neopentyl, hexyl, 1-methylpentyl,

3-methylpentyl. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. The term "aryl" is intended to include phenyl and naphthyl. The term "halo", unless otherwise indicated, includes bromo, chloro, fluoro and iodo. The term "cycloalkyl" is intended to 5 include cycloalkyl groups having 3-7 carbon atoms. With reference to substituents, the term "independently" means that when more than one of such substituent is possible, such substituents may be the same or different from each other.

10 Those compounds of the present invention which contain a basic moiety can be converted to the corresponding acid addition salts by techniques known to those skilled in the art. Suitable acids which can be employed for this purpose include hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, pyruvic, oxalic, malonic, succinic, 15 maleic, fumaric, malic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, 2-phenoxybenzoic, 2-acetoxybenzoic, or saccharin, and the like. In general, the acid addition salts can be prepared by reacting the free base of compounds of formula 1 with the acid and isolating the salt.

20 Pharmaceutical compositions containing one or more of the compounds of the invention described herein as the active ingredient can be prepared by intimately mixing the compound or compounds with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The 25 carrier may take a wide variety of forms depending upon the desired route of administration (e.g., oral, parenteral). Thus for liquid oral preparations such as suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, stabilizers, coloring agents and the like; for solid oral preparations, such as powders, 30 capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Solid oral preparations may also be coated with substances such as sugars or be enteric-coated so as to modulate major site of absorption. For

parenteral administration, the carrier will usually consist of sterile water and other ingredients may be added to increase solubility or preservation. Injectable suspensions or solutions may also be prepared utilizing aqueous carriers along with appropriate additives.

5

For the treatment of disorders of the central nervous system, the pharmaceutical compositions described herein will typically contain from 1 to about 1000 mg of the active ingredient per dosage; one or more doses per day may be administered. Determination of optimum doses and frequency of 10 dosing for a particular disease state or disorder is within the experimental capabilities of those knowledgeable in the treatment of central nervous system disorders. The preferred dose range is 1-100 mg/kg.

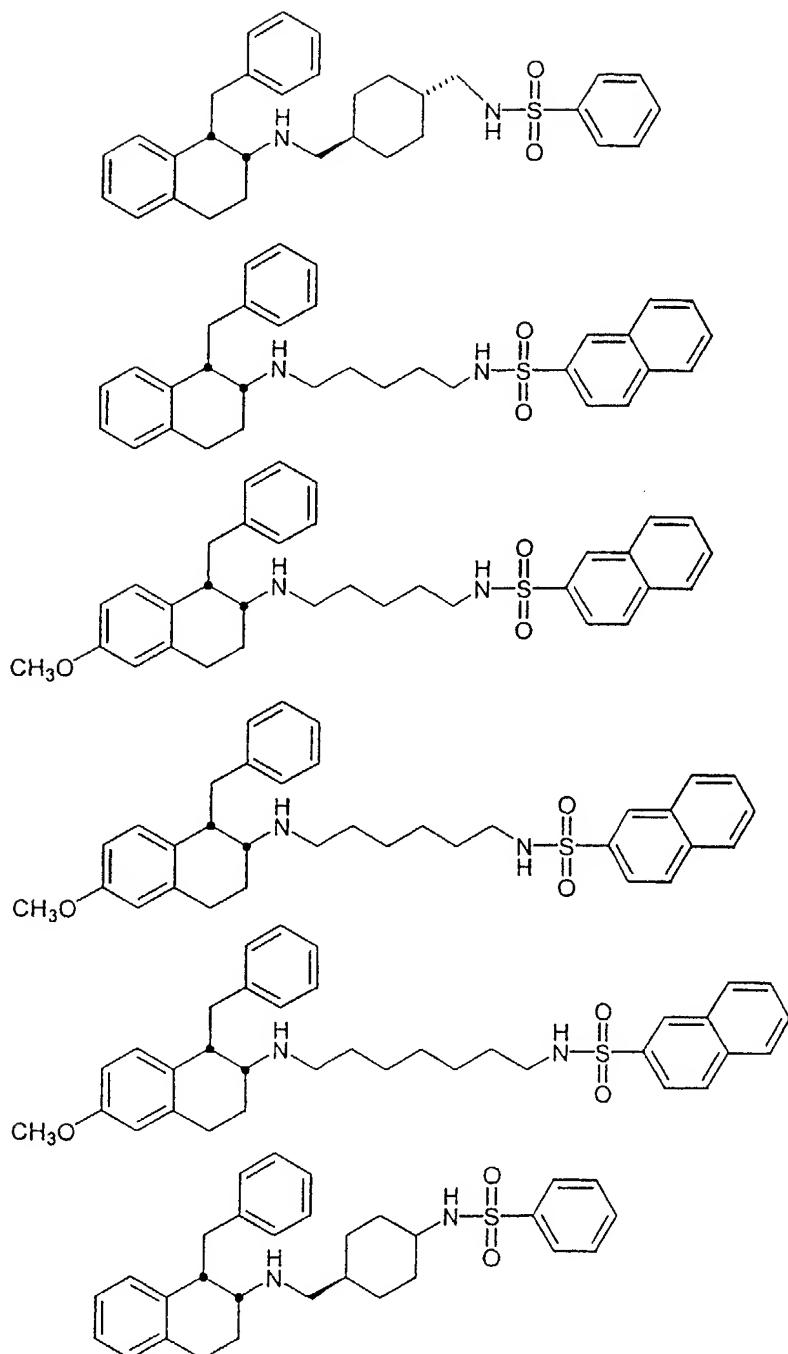
As modulators of the NPY5 receptor, the compounds of Formula 1 are 15 useful for treating feeding disorders such as obesity, anorexia nervosa and bulimia nervosa, and abnormal conditions such as epilepsy, depression, anxiety and sexual / reproductive disorders in which modulation of the NPY5 receptor may be useful. The compounds compete with the endogenous ligands NPY and PYY and possibly non-endogenous ligands, and bind to the 20 NPY5 receptor. In addition, the compounds demonstrate antagonist activity by antagonizing the action of NPY upon binding to the Y5 receptor.

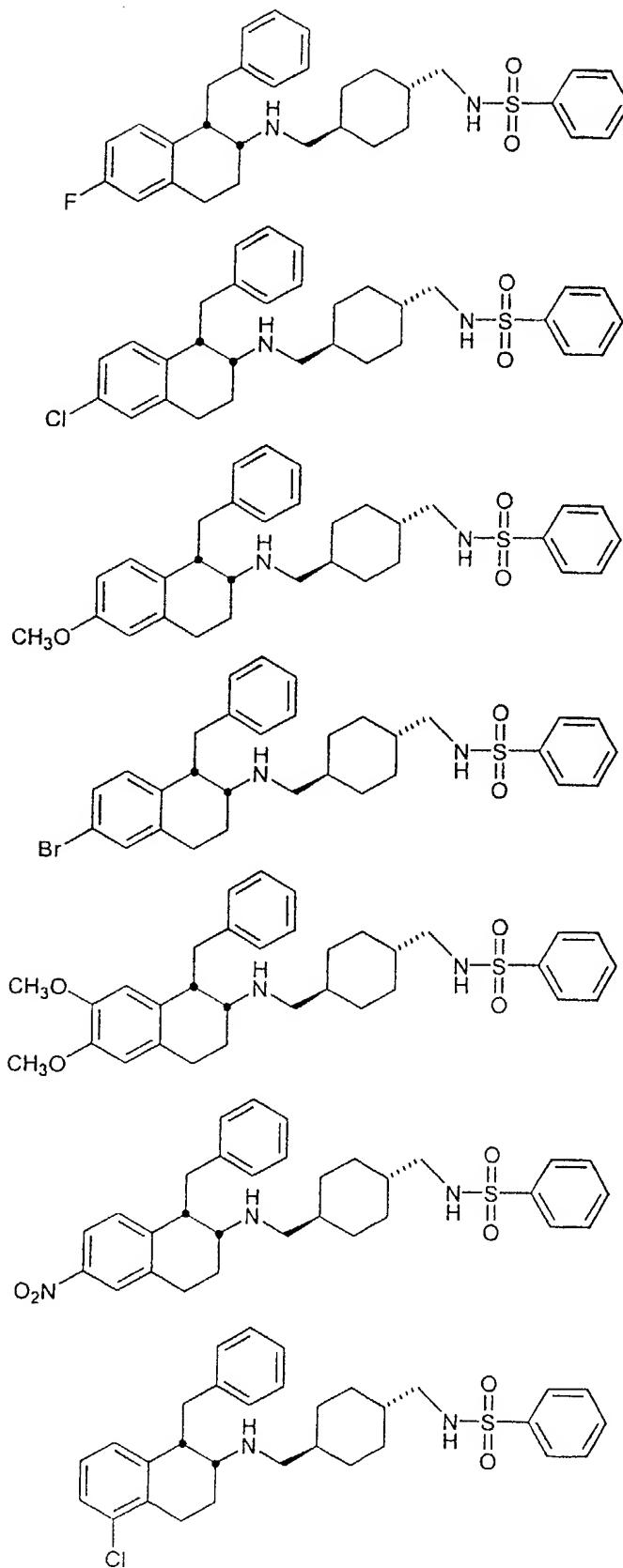
The compounds described herein are ligands of the NPY5 receptor, but are not necessarily limited solely in their pharmacological or biological action 25 due to binding to this or any neuropeptide, neurotransmitter or G-protein coupled receptor. For example, the described compounds may also undergo binding to dopamine or serotonin receptors. The compounds described herein are potentially useful in the regulation of metabolic and endocrine functions, particularly those associated with feeding, and as such, may be useful for the 30 treatment of obesity. In addition, the compounds described herein are potentially useful for modulating other endocrine functions, particularly those controlled by the pituitary and hypothalamic glands, and therefore may be

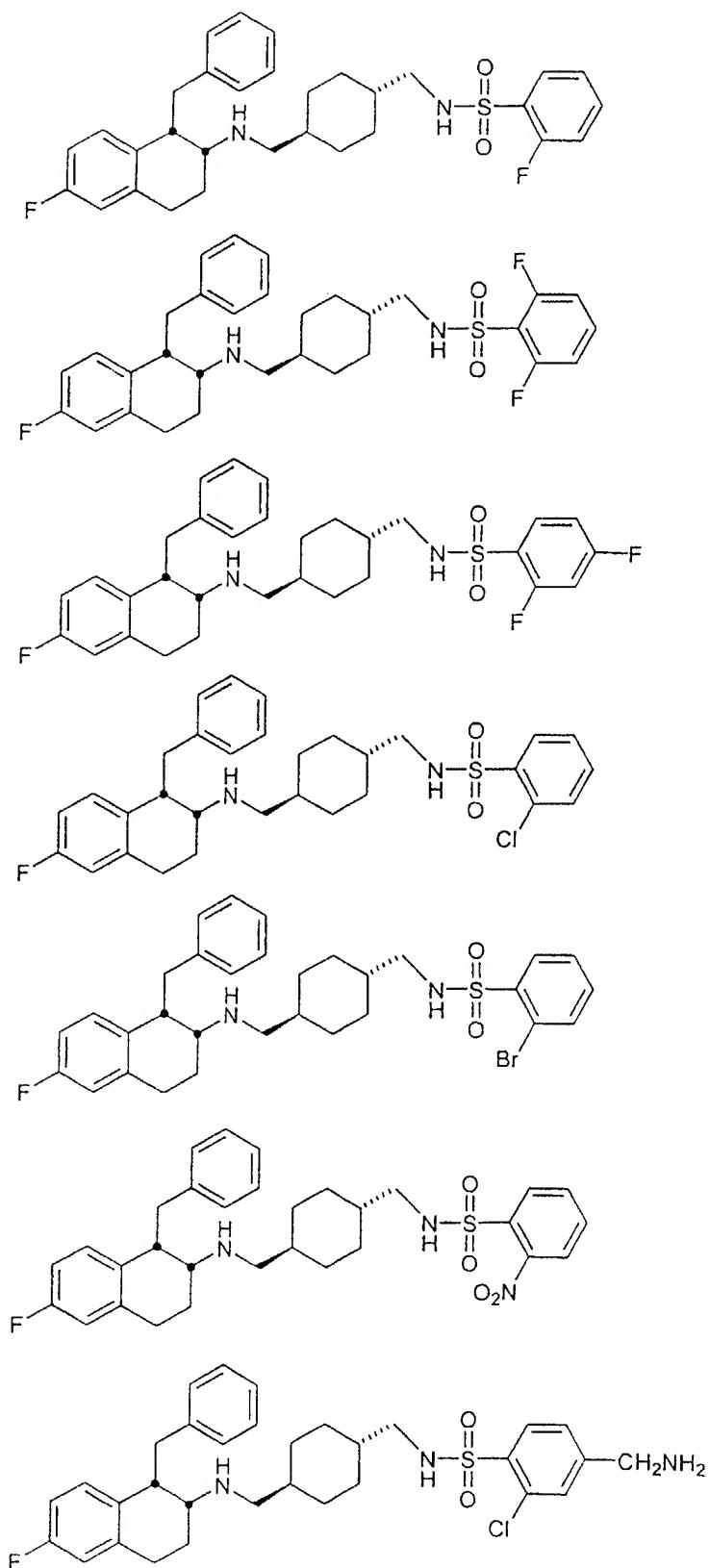
useful for the treatment of inovulation/infertility due to insufficient release of luteinizing hormone (LH).

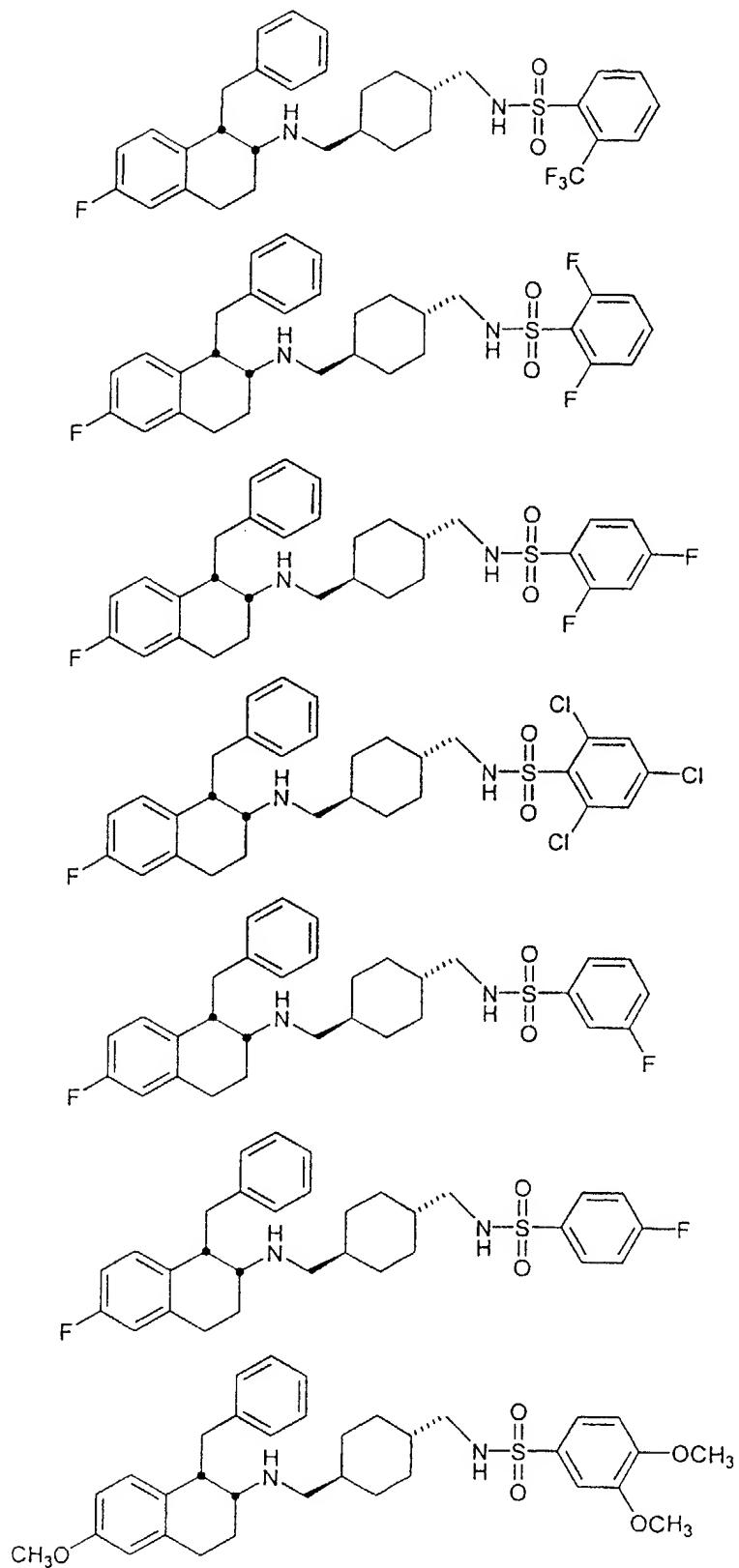
The present invention comprises pharmaceutical compositions
5 containing one or more of the compounds of Formula 1. Amide precursors to compounds of Formula 1 are also novel and are considered to be part of the invention.

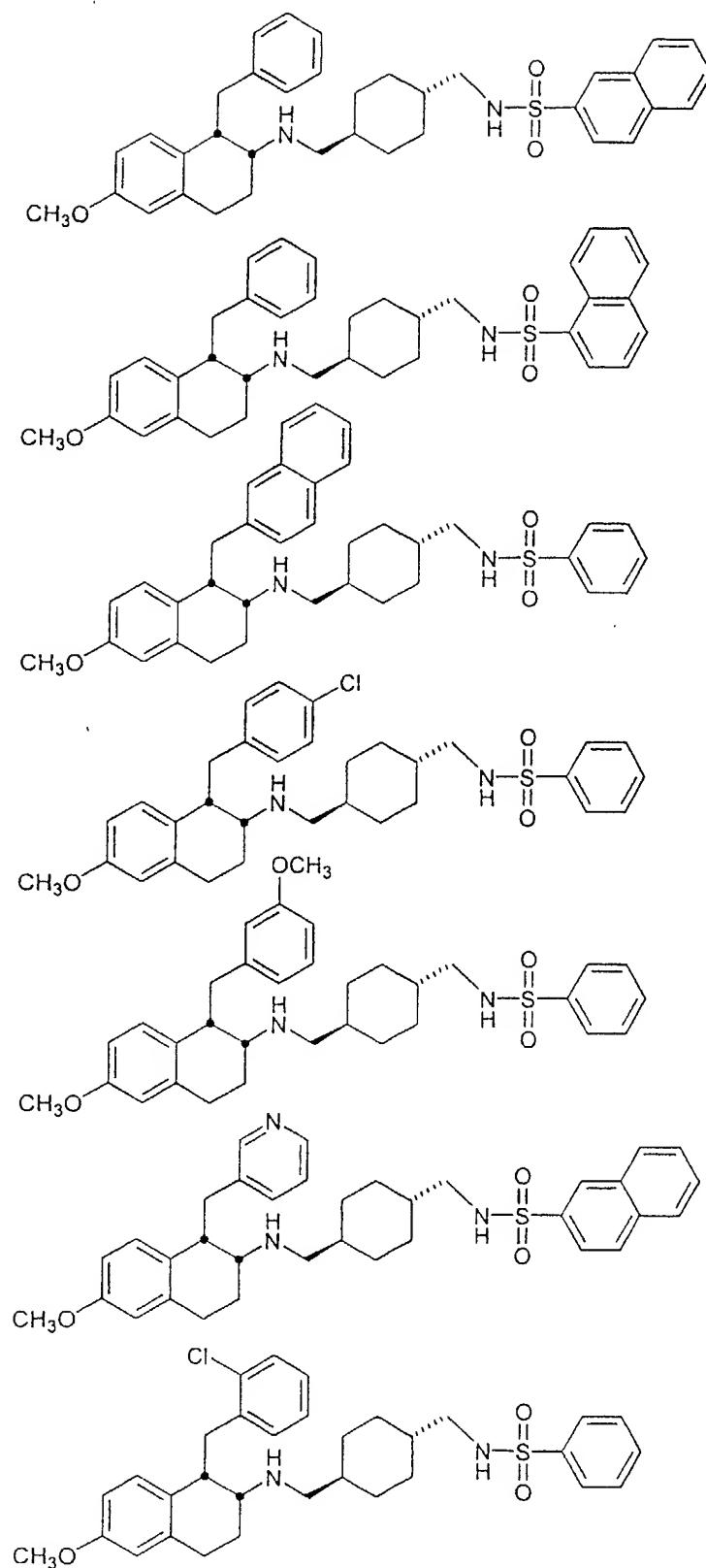
Examples of particularly preferred compounds of formula 1 include:

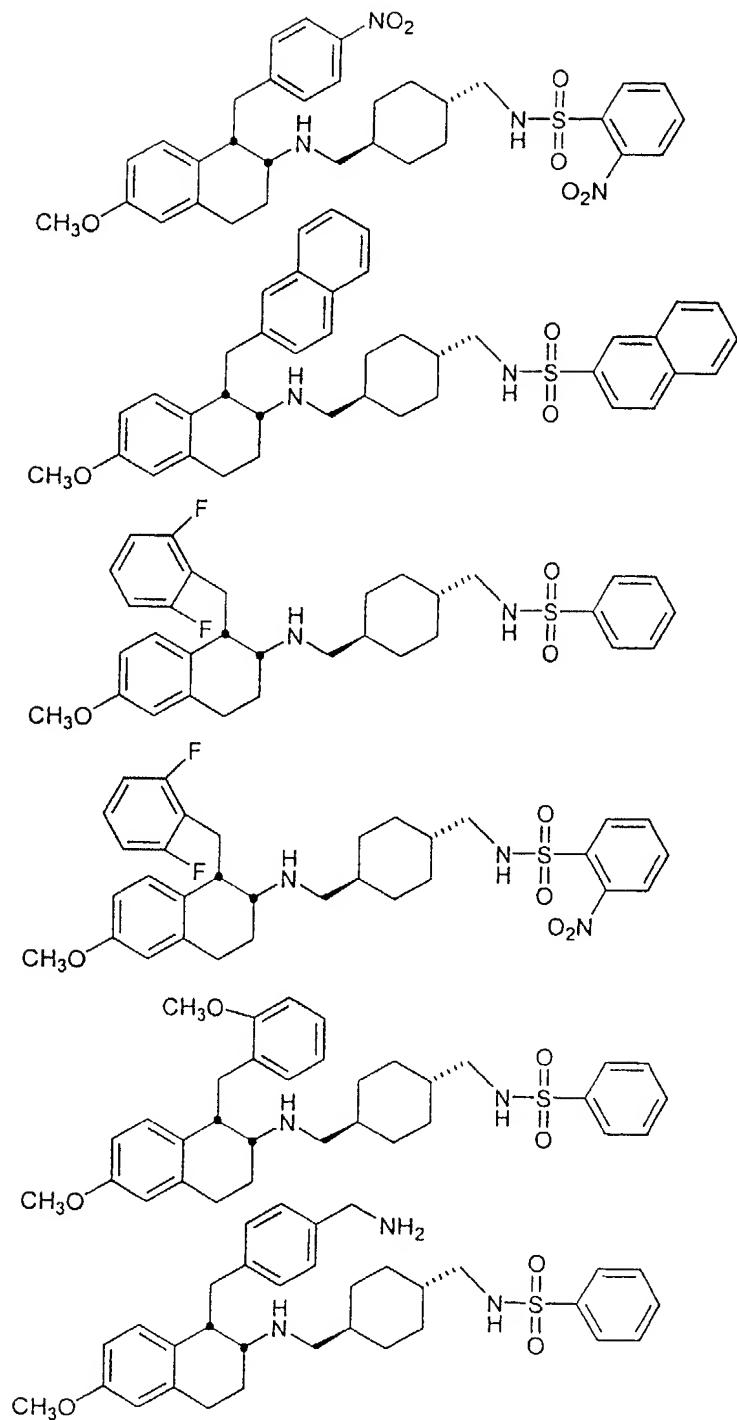


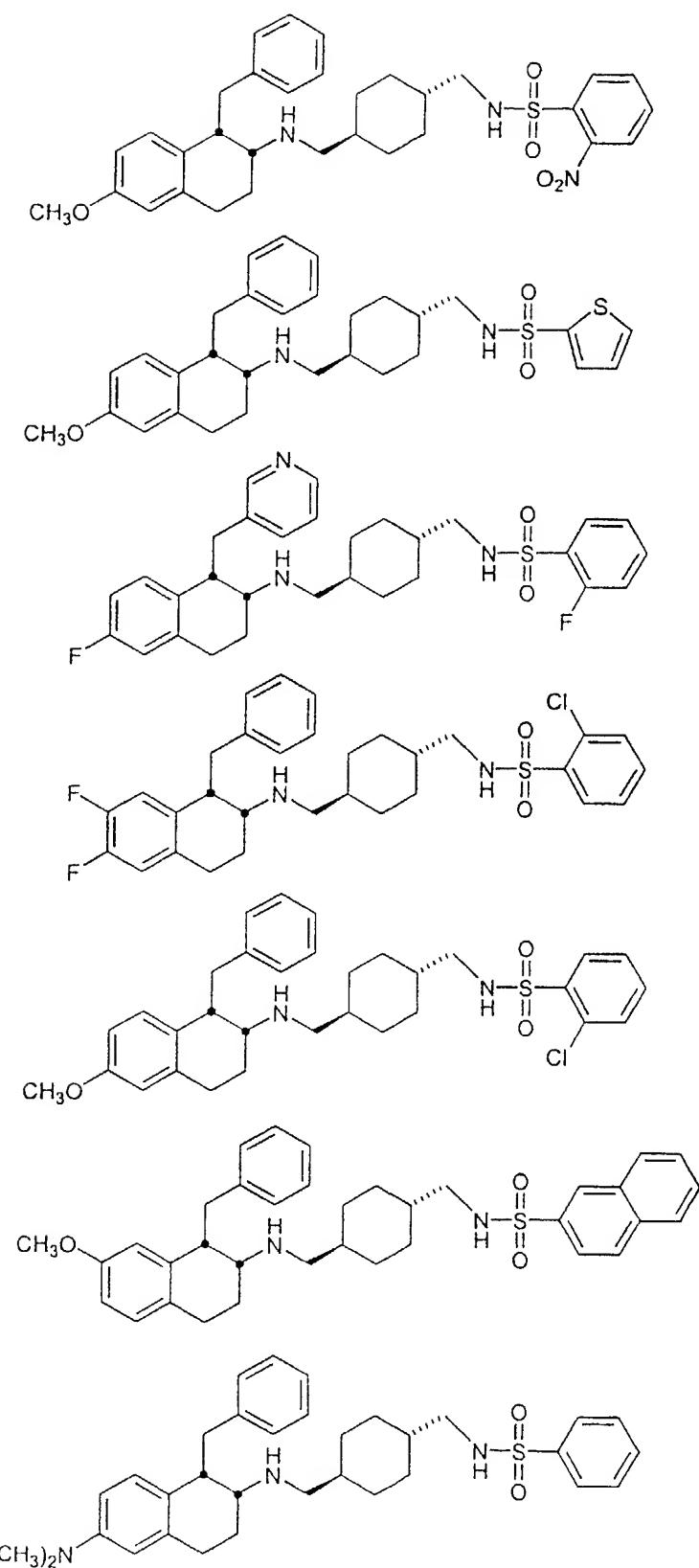


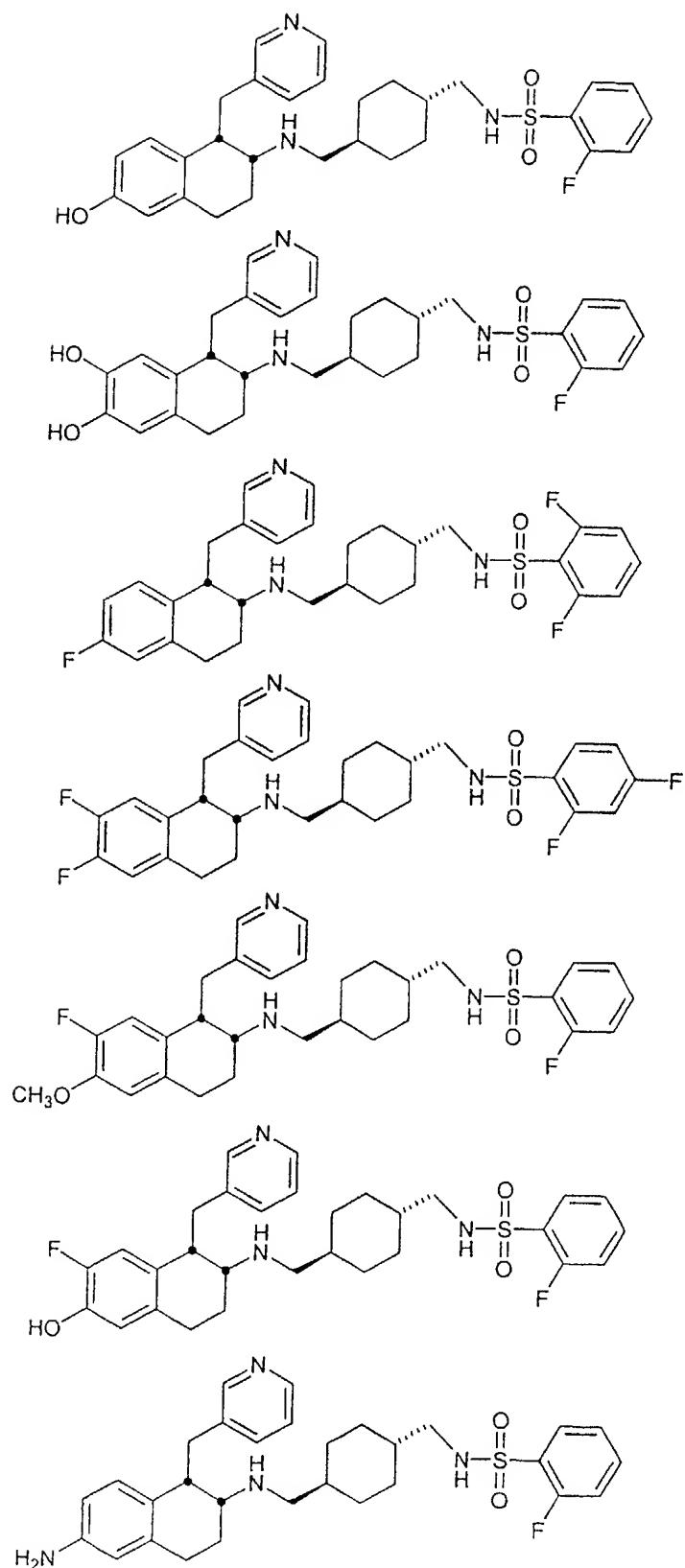


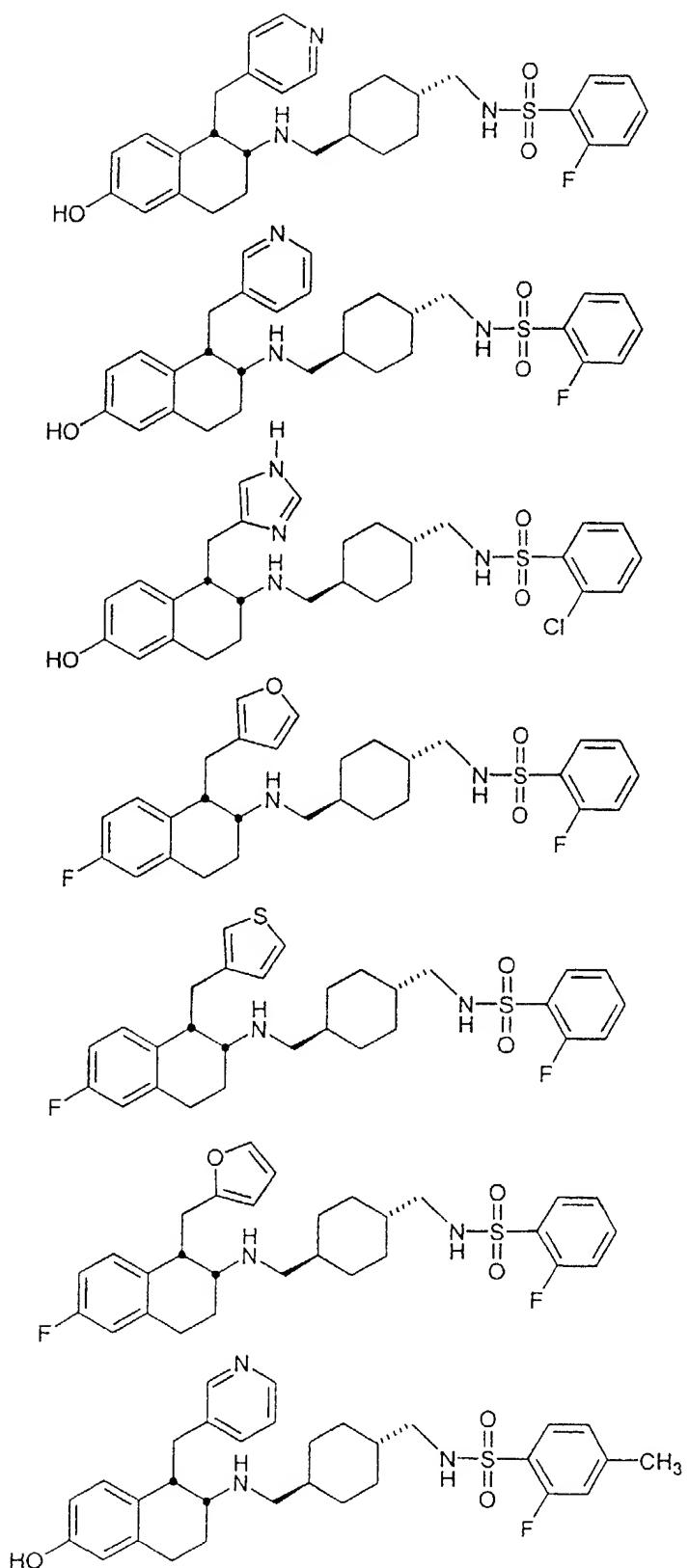


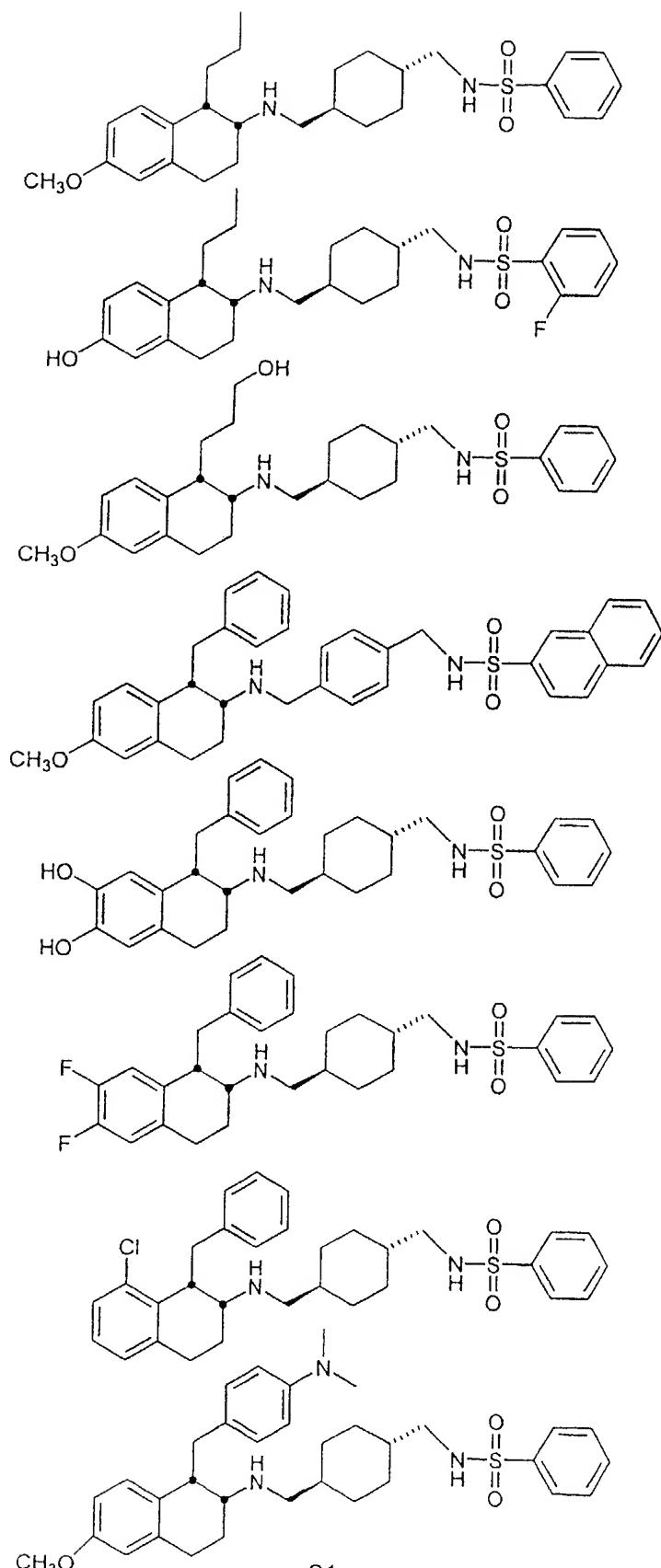


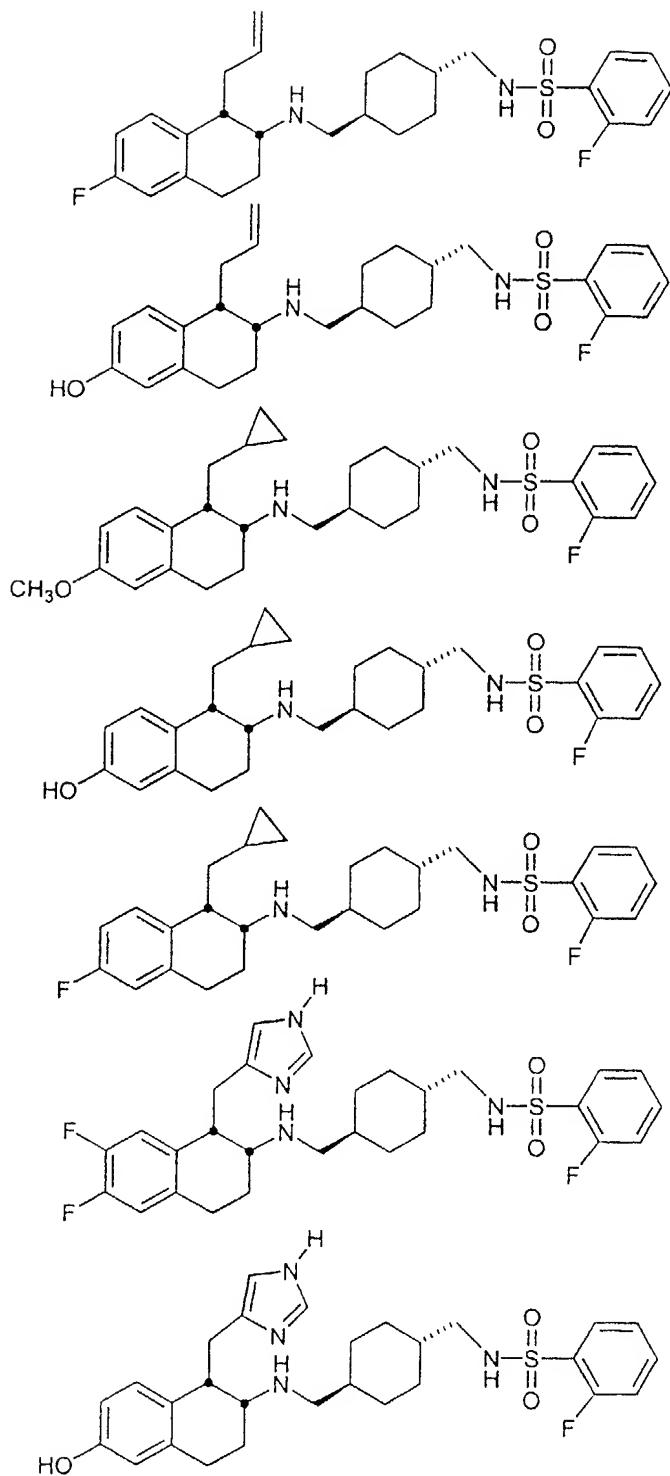


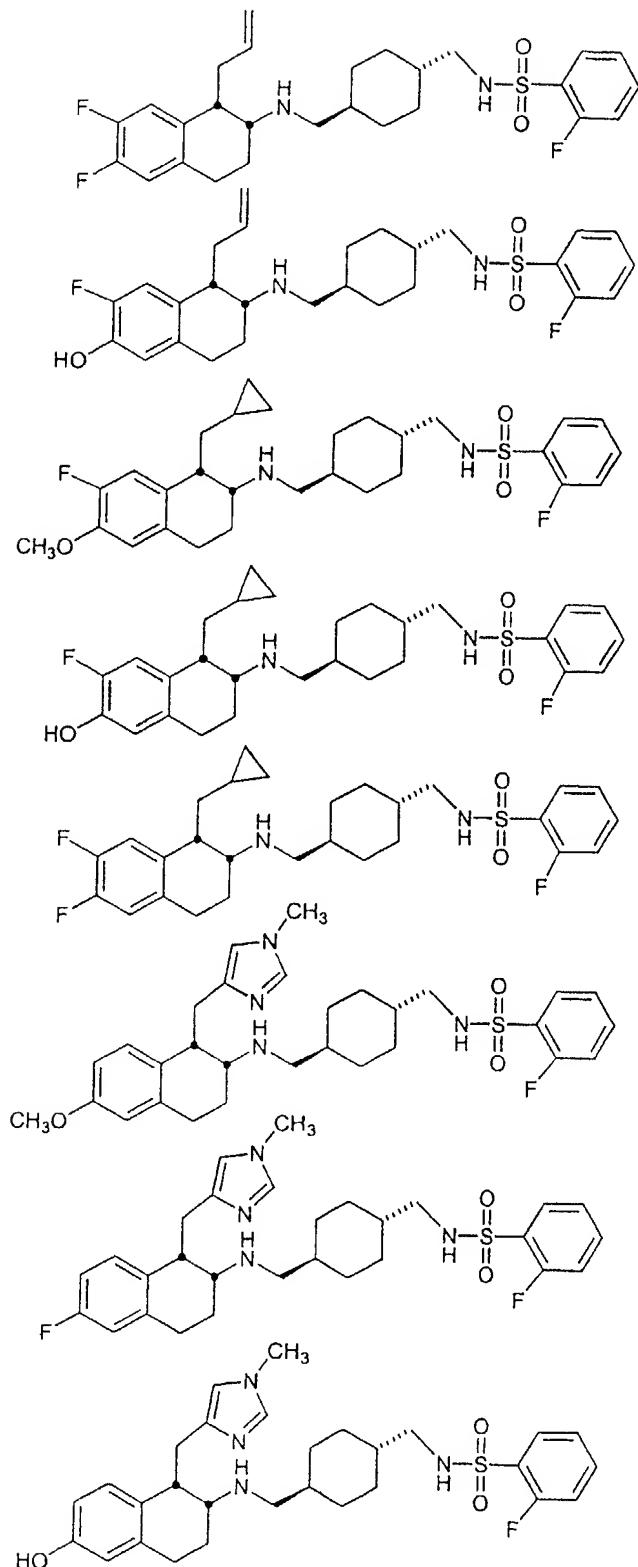


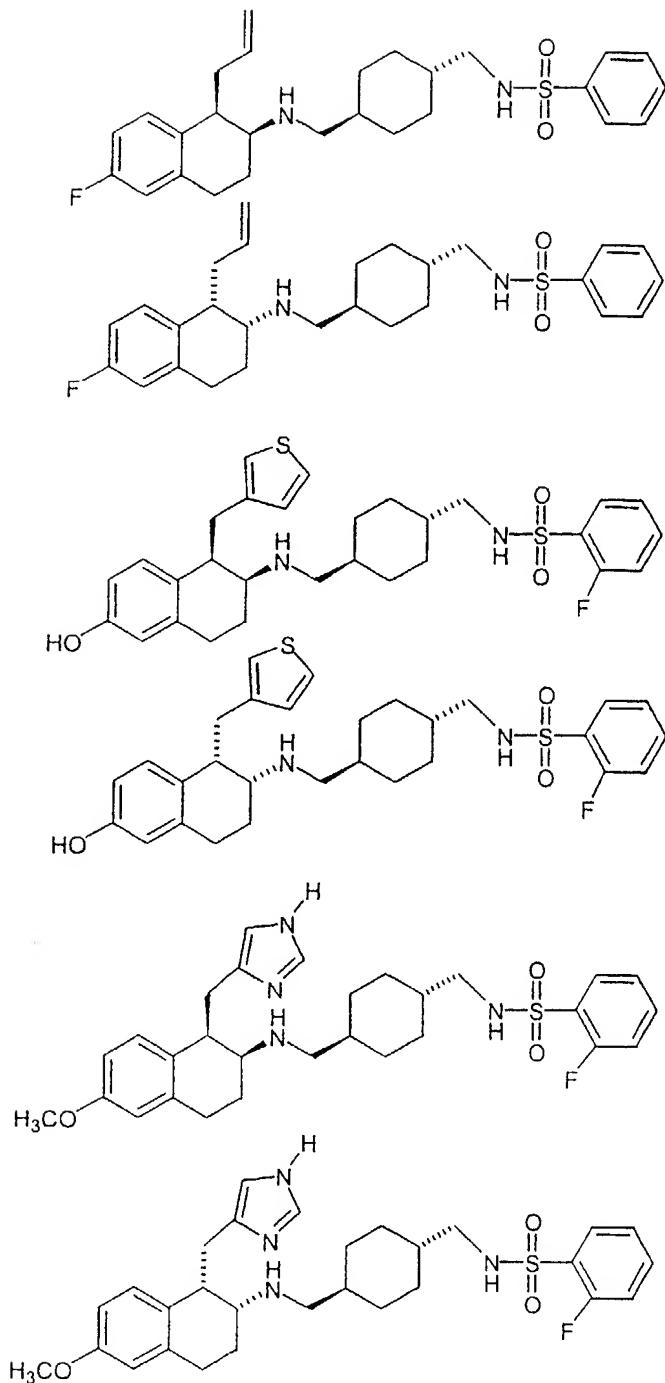












DETAILED DESCRIPTION OF THE INVENTION

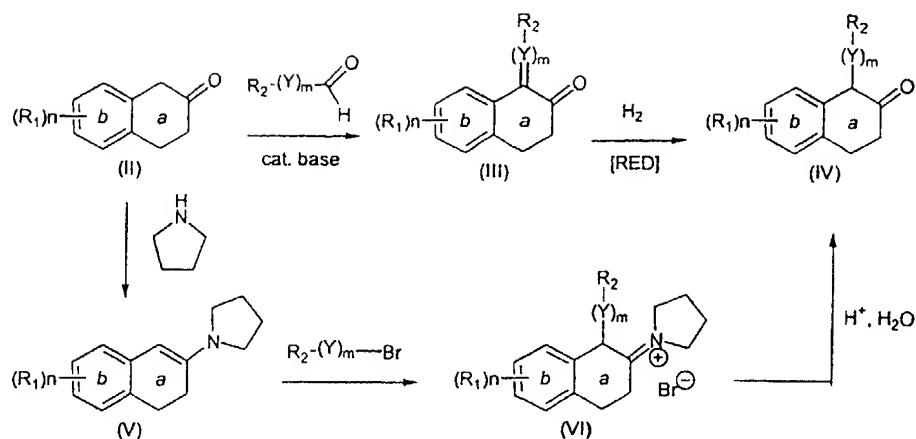
The N-substituted aminotetralins of formula 1 that comprise this
5 invention are synthesized via several distinct chemical syntheses as outlined in
Schemes 1-5; each synthetic route consists of several sequential chemical
operations that can be generalized as described below:

- Introduction of the α -substituent onto the tetralone nucleus
- 10 • Conversion to the corresponding α -substituted- β -aminotetralin
- Acylation of the aminotetralin
or reductive amination of the α -substituted- β -tetralone
- Reduction to re-generate the aminotetralin system (if needed)
and / or
- 15 • Sulfenylation (if needed)
(protecting group manipulations may be needed at various stages)

It is generally preferred that the respective product of each process step
be separated from other components of the reaction mixture and subjected to
20 purification before its use as a starting material in a subsequent step.
Separation techniques typically include evaporation, extraction, precipitation
and filtration. Purification techniques typically include column chromatography
(Still, W. C. et. al., *J. Org. Chem.* 1978, 43, 2921), thin-layer chromatography,
crystallization and distillation. The structures of the final products,
25 intermediates and starting materials are confirmed by spectroscopic,
spectrometric and analytical methods including nuclear magnetic resonance
(NMR), mass spectrometry (MS) and liquid chromatography (HPLC). In the
descriptions for the preparation of compounds of this invention, ethyl ether,
tetrahydrofuran and dioxane are common examples of an ethereal solvent;
30 benzene, toluene, hexanes and cyclohexane are typical hydrocarbon solvents
and dichloromethane and dichloroethane are representative halohydrocarbon
solvents. In those cases wherein the product is isolated as the acid addition
salt the free base is obtained by techniques known to those skilled in the art.

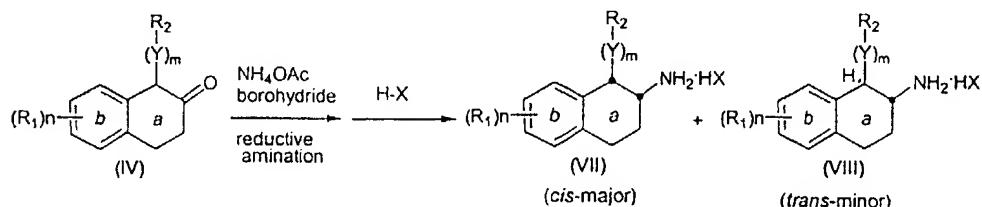
Specifically, an appropriately substituted β -tetralone (II) is reacted with an aryl or heteroaryl aldehyde in the presence of a base such as piperidine, in an inert halohydrocarbon, ethereal or hydrocarbon solvent, such as benzene, from ambient temperature to reflux, to afford the corresponding α -benzylidene- β -tetralone or α -heteroarylmethylidene- β -tetralone (III). The β -tetralone (III) is dissolved in an inert hydrocarbon, ethereal, ester or alcohol solvent, such as methanol, and reacted with hydrogen gas from ambient pressure to about 100 p.s.i. in the presence of a suitable catalyst such as palladium on carbon. The reaction is performed at a temperature from ambient temperature to reflux, to yield the desired α -substituted- β -tetralone product (IV) (Scheme 1).

An alternative method for the preparation of α -substituted- β -tetralones (IV) involves the reaction of an appropriately substituted β -tetralone (II) with a base such as pyrrolidine in an inert halohydrocarbon solvent such as dichloromethane or hydrocarbon solvent such as benzene, under Dean-Stark conditions (removal of water) or in an alcohol solvent such as methanol, at a temperature from ambient temperature to reflux, to afford enamine (V). Alkylation of enamine (V) is accomplished by reaction with a benzylic, heterocyclicalkyl or an allylic halide in an inert solvent such as acetonitrile, at a temperature from ambient temperature to reflux, to afford the α -substituted- β -iminium salt (VI). Hydrolysis of the salt (VI) to produce the desired α -substituted- β -tetralone product (IV) is accomplished by reaction of (VI) with water and an inorganic or organic acid such as hydrochloric or glacial acetic acid in an inert hydrocarbon, ethereal, alcohol or halohydrocarbon solvent, or a mixture thereof, such as methanol and dichloromethane (Scheme 1).



Scheme 1

The α -substituted- β -tetralones (IV) are converted to the corresponding
 5 aminotetralins via reaction with an ammonium salt such as ammonium acetate
 in the presence of a reducing agent such as sodium cyanoborohydride, for
 example, in an inert halohydrocarbon, hydrocarbon, ethereal or alcohol solvent
 such as methanol to produce the *cis*-aminotetralin (VII). In some cases, the
 10 *trans*-aminotetralin (VIII) is also formed as a minor product. The *cis*-
 aminotetralins (VII) can also be isolated as acid addition salts by treatment with
 an organic or an inorganic acid, such as trifluoroacetic acid or hydrochloric
 acid, for example (Scheme 2).

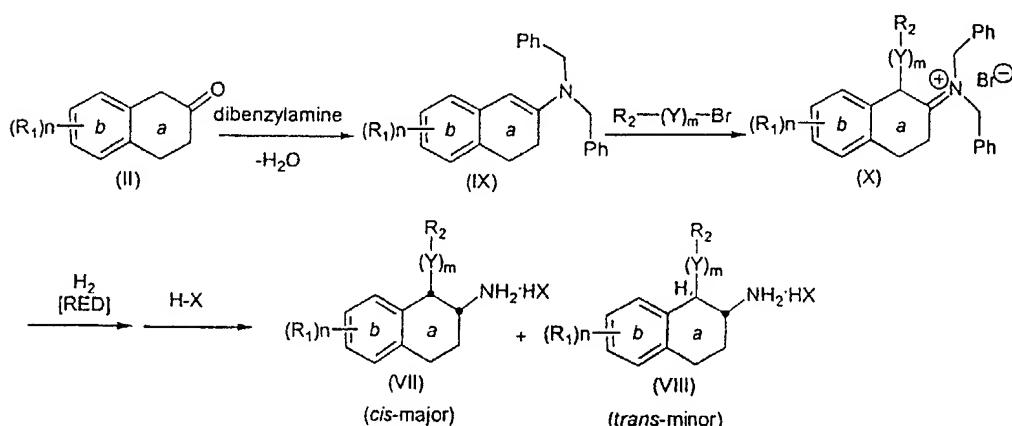


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Scheme 2

An alternative method for the preparation of the α -substituted- β -
 aminotetralins (VII) consists of reacting an appropriately α -substituted- β -
 20 tetralone with dibenzylamine in an inert halohydrocarbon, ethereal, alcohol or
 hydrocarbon solvent, such as benzene, under Dean-Stark conditions (removal
 of water), to afford enamine (IX). Alkylation of the enamine (IX) is
 accomplished via reaction with a benzylic or heterocyclicalkyl halide in an inert

solvent such as acetonitrile, at a temperature from ambient temperature to reflux, to afford the α -substituted- β -iminium salt (X). The iminium salt (X) is dissolved in an inert hydrocarbon, ethereal or ester solvent such as ethyl acetate or alcohol solvent such as methanol and reacted with hydrogen gas at 5 a pressure from ambient pressure to 100 p.s.i. in the presence of a suitable catalyst such as palladium on carbon, at a temperature from ambient temperature to reflux, to yield the desired β -aminotetralin (VII) (Scheme 3).



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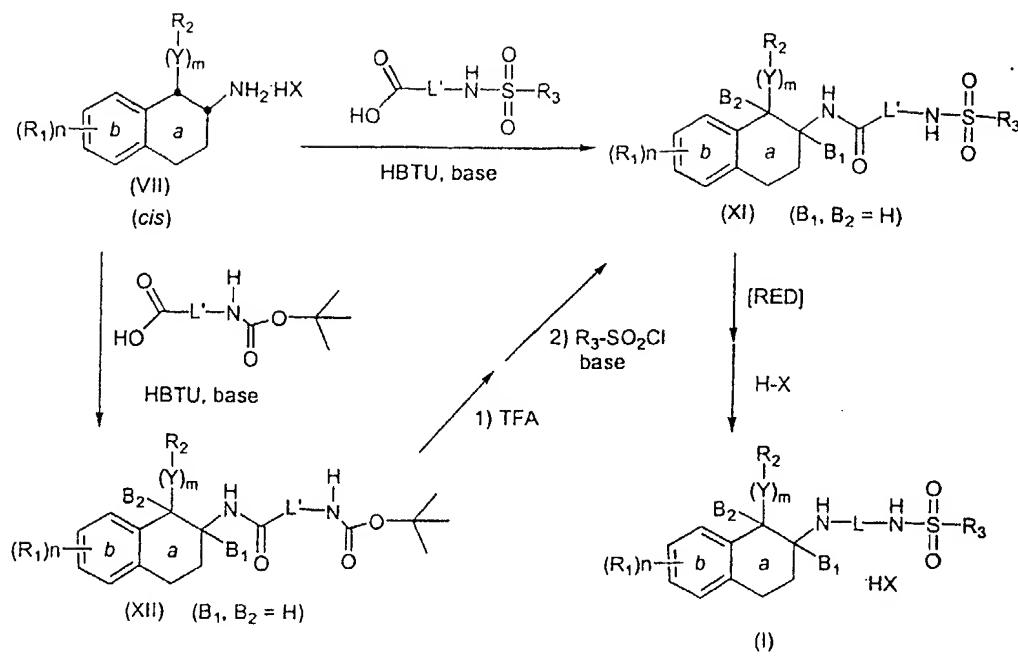
Scheme 3

The β -aminotetralins described above are acylated via suitable amidation methods (see Gross and Meienhofer, Eds., "The Peptides", Vols. 1-15 3, Academic Press, New York, NY, 1979-1981). A carboxylic acid is converted to an activated ester via peptide coupling methods known to those skilled in the art, and subsequently reacted with an aminotetralin (VII) to afford the corresponding amide product. For example, a carboxylic acid such as *trans*-4-(2-naphthylsulfonamido)methylcyclohexane carboxylic acid or 4-(*tert*-20 butoxycarbonyl)aminomethylcyclohexane carboxylic acid is reacted with HBTU (2-(1H-benzotrazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate and a β -aminotetralin (VII) in the presence of a base such as diisopropylethylamine, in an inert solvent such as N,N-dimethylformamide, at a temperature from ambient temperature to reflux, to afford amide (XI) or (XII) 25 respectively. Cleavage of the BOC (butoxycarbonyl) protecting group with

trifluoroacetic acid produces the free amine, which is sulfonylated to yield amide (XI).

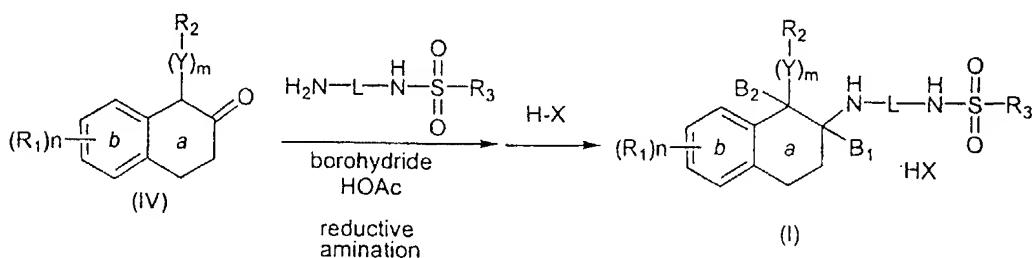
Alternatively, the sulfonamido-carboxylic acid is treated with an amine
5 base, such as triethylamine, in an inert hydrocarbon, ethereal or halohydrocarbon solvent, such as dichloroethane, and subsequently reacted with isobutyl chloroformate at a temperature from about -20°C to 80°C. This mixture is then reacted with β -aminotetralin (VII), in suitable inert solvent such a dichloromethane at a temperature from about -20°C to reflux, affords the
10 tetralinamide (XI).

The N-substituted aminotetralin compounds (I) of the invention are prepared via reduction of tetralinamide (XI) by reaction with a suitable reducing agent such as borane-tetrahydrofuran complex or lithium aluminum hydride in
15 an inert hydrocarbon solvent such as toluene or ethereal solvent such as tetrahydrofuran, at a temperature from ambient temperature to reflux. The final product can be isolated as an acid addition salt upon treatment with a suitable organic acid such as trifluoroacetic acid or inorganic acid such as hydrochloric acid (Scheme 4).



Scheme 4

5 An alternative method for the synthesis of N-substituted aminotetralins (I) entails the reaction of an appropriately α -substituted β -tetralone (IV) with an amine ($\text{H}_2\text{N-L-NHSO}_2-\text{R}_3$) in the presence of a reducing agent such as sodium borohydride, or sodium triacetoxyborohydride, for example, in an inert ethereal, halohydrocarbon, or alcohol solvent such as dichloromethane or methanol
 10 respectively, at a temperature from ambient temperature to reflux, to yield the desired N-substituted aminotetralin product (I) (Scheme 5).



15 Scheme 5

In the above reaction schemes, X is halo such as chloro, bromo and iodo and Ph is phenyl.

EXAMPLES

The following examples describe the invention in greater detail and are intended to illustrate the invention, but not to limit it. All compounds were identified by a variety of methods including nuclear magnetic resonance spectroscopy, mass spectrometry and in some cases, infrared spectroscopy and elemental analysis. Nuclear magnetic resonance (300 MHz NMR) data is reported in parts per million downfield from tetramethylsilane. Mass spectra data is reported in mass/charge (m/z) units. Unless otherwise noted, the materials used in the examples were obtained from readily available commercial sources or synthesized by standard methods known to those skilled in the art.

15

EXAMPLE 1

rac-[1 α ,2 α (*trans*)]-N-[[[[1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] 2-naphthalenesulfonamide (10)

20

A. 6-Methoxy- β -tetralone **1** (3.0 g, 17.0 mmol) was placed in a 250 mL round-bottom flask and dissolved in benzene (90 mL). Pyrrolidine (2.4 mL, 28.8 mmol) was added with stirring and the flask was flushed with argon. A Dean-Stark trap and a reflux condenser were attached and the solution was heated at reflux for 67 hours. After cooling, the solvent was removed *in vacuo* to yield enamine **2** as a orange glassy solid which was used in subsequent reactions without further purification. MS (MH $^+$) 230; 1 H NMR ($CDCl_3$) δ 1.92 (m, 4 H), 2.45 (t, 2H), 2.84 (t, 2H), 3.26 (m, 4H), 3.79 (s, 3H), 5.11 (s, 1H), 6.65 (m, 2H), 6.81 (m, 1H).

25

B. Enamine **2** was dissolved in acetonitrile (90 mL) in a 250 mL round-bottom flask and benzyl bromide (3.4 mL, 29 mmol) was added to this solution with stirring. The flask was flushed with argon and a reflux condenser was

attached. The solution was heated at reflux for 19 hours. After cooling, the solvents were removed *in vacuo*, the resulting orange glassy solid was titurated with ethyl ether and filtered repeatedly until all traces of the benzyl bromide had been removed. The resulting iminium salt 3 was used in the next 5 step without further purification. MS (MH⁺) 320.

C. The iminium salt 3 from the previous reaction was transferred to a 500 mL Erlenmeyer flask and methanol (100 mL), dichloromethane (50 mL), water (50 mL), and glacial acetic acid (3 mL) were added. The resulting mixture was 10 flushed with nitrogen, capped, and stirred for 14 hours. The solvents were removed *in vacuo*. The resulting oil was dissolved in ethyl acetate (250 mL) and washed with water (4 x 100 mL). The organic extract was dried over magnesium sulfate, filtered, and the solvents removed *in vacuo* to yield an oily 15 crude product. This material was purified via chromatography (silica gel column (dimensions 2.5 x 27 cm); 25% ethyl acetate:75% hexanes (v/v) as the eluent). After evaporation of the appropriate fractions, 3,4-dihydro-6-methoxy-1-(phenylmethyl)-2(1H)-naphthalenone 4 was obtained as a thick yellow oil (2.13 g, 8.0 mmol). MS (MH⁺) 267; ¹H NMR (CDCl₃) δ 2.43-2.60 (m, 3H), 2.75-2.81 (m, 1H), 3.18 (dd, 1H), 3.68 (dd, 2H), 3.79 (s, 3H), 6.58-6.91 (m, 5H), 20 7.15 (m, 3H). (Figure 1).

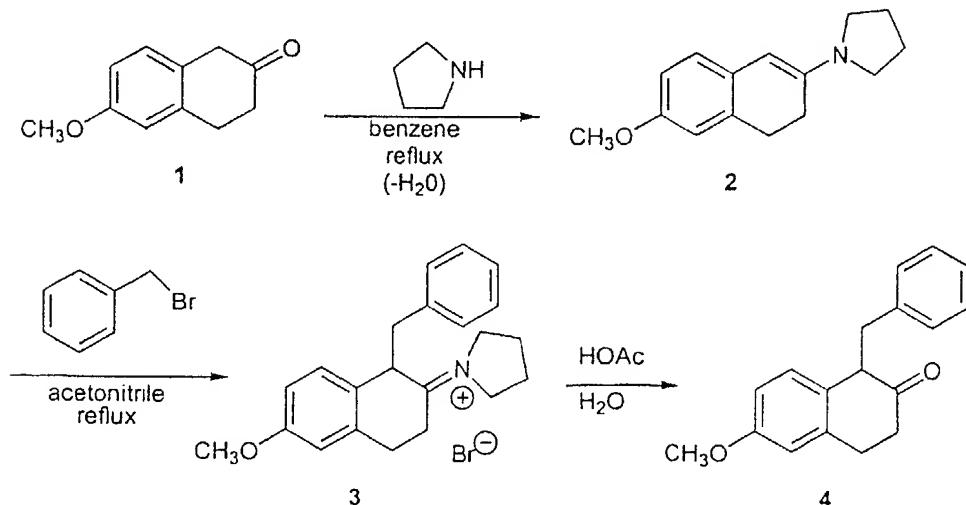


Figure 1

Alternatively, 3,4-dihydro-6-methoxy-1-(phenylmethyl)-2(1H)-naphthalenone 4 is prepared as follows:

5 6-Methoxy- β -tetralone 1 (1.0 g, 5.7 mmol) was dissolved in benzene (25 mL) with stirring in a 50 mL round-bottom flask. To this solution, benzaldehyde (0.60 mL, 5.9 mmol) was added followed by catalytic piperidine (0.014 mL, 0.14 mmol). The flask was flushed with argon and a reflux condenser equipped with a Dean-Stark trap was attached. The solution was heated at
10 reflux for 28 hours and then cooled to room temperature. The solvent was removed *in vacuo* to yield a dark orange oil. This crude product was dissolved in ethyl ether (100 mL) and then washed with 3N HCl (2 x 50 mL), water (1 x 50 mL), and lastly with saturated brine solution (1 x 50 mL). The organic extract was dried over magnesium sulfate, filtered, and the solvents removed
15 *in vacuo*. The resultant oil was purified via column chromatography (silica gel column (dimensions 5 x 25 cm); 25% ethyl acetate:75% hexanes (v/v) as the eluent). After evaporation of the appropriate fractions, 3,4-dihydro-6-methoxy-1-(phenylmethylidienyl)-2-naphthalenone 5 was obtained as a pale yellow oil (0.70 g, 2.6 mmol) which solidified upon storage in a refrigerator. MS (MH⁺)
20 265; ¹H NMR (CDCl₃) δ 2.54 (t, 2H), 2.98 (t, 2H), 3.79 (s, 3H), 6.63 (dd, 1H), 6.96 (d, 1H), 7.12 (d, 1H), 7.29 (m, 3H), 7.40-7.48 (m, 3H).

Compound 5 (0.464 g, 1.8 mmol) was placed in a 250 mL Parr shaker bottle and dissolved in ethyl acetate (25 mL). Separately, 10% palladium on carbon (0.029 g) was placed in a vial and to it was added methanol (25 mL) in order to create a slurry. This material was then carefully added to the Parr vessel and the mixture was hydrogenated under a pressure of approximately 50 psi for 19 hours. The reaction solution was filtered over a pad of Celite. The solvents were removed *in vacuo* and the resulting oil was purified by
25 column chromatography (silica gel column (dimensions 2.5 x 26 cm); 25% ethyl acetate:75% hexanes (v/v) as the eluent). After evaporation of the appropriate fractions, 3,4-dihydro-6-methoxy-1-(phenylmethyl)-2(1H)-

naphthalenone 4 was obtained as an off-white oil (0.40 g, 1.50 mmol) (Figure 2).

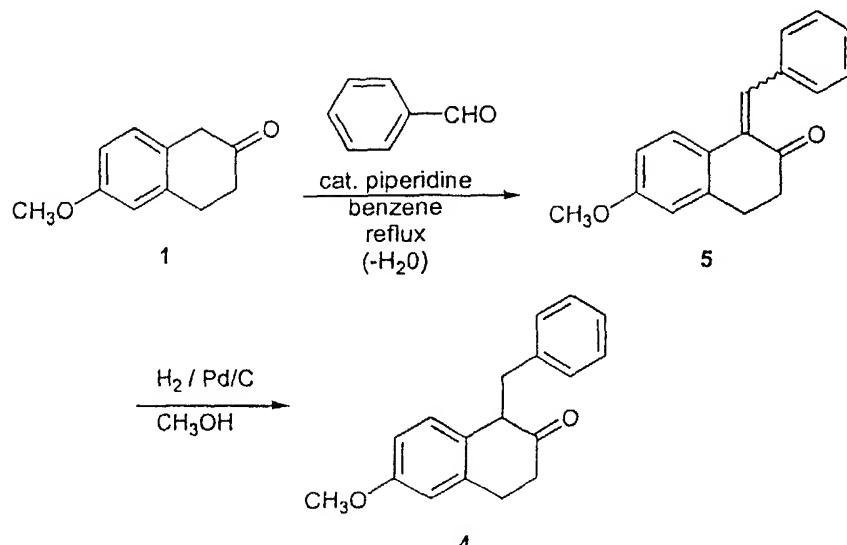


Figure 2

5

- D. Ammonium acetate (10.7 g, 138 mmol) was added to a solution of 3,4-dihydro-6-methoxy-1-(phenylmethyl)-2(1H)-naphthalenone 4 (3.64 g, 13.6 mmol) in methanol (530 mL) in a 1 L round-bottom flask with vigorous stirring. Sodium cyanoborohydride (4.29 g, 68.3 mmol) was added and the flask was flushed with argon. A condenser was attached, and the solution was heated at reflux for 21 hours. The solution was cooled to room temperature and the solvents were removed *in vacuo*. The cream colored solid was dissolved in a mixture of ethyl ether (600 mL) and 0.1 M sodium hydroxide solution (225 mL). The aqueous phase was removed and the organics were washed with an additional 0.1 M sodium hydroxide solution (1 x 225 mL), and then with water (1 x 200 mL). The combined aqueous extracts were back extracted with ethyl ether (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvents were removed *in vacuo* to afford *cis*-1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenamine 6. The crude product was dissolved in ethyl ether (75 mL) and an excess of 1 M hydrogen chloride in ethyl ether was added. This resulted in a precipitate of the product as a HCl salt. The ethyl ether was removed *in vacuo* and any
- 10
15
20

large chunks were crushed with a spatula. Ethyl acetate (25 mL) was added, the resultant slurry was heated to reflux and then cooled to room temperature. The solids were filtered off and rinsed with a small portion of ethyl acetate and then with ethyl ether and dried via aspiration to afford *cis*-1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenamine hydrochloride **6a** as an off-white powder (2.13 g, 7.0 mmol). MS (MH⁺) 268; ¹H NMR (CDCl_3) δ 2.05-2.30 (m, 2H), 2.50-2.60 (m, 1H), 2.83-3.03 (m, 3H), 3.30-3.40 (m, 2H), 3.71 (s, 3H), 6.00 (d, 1H), 6.35 (dd, 1H), 6.60 (d, 1H), 7.02-7.16 (m, 5H), 8.53 (bs, 1H), 8.96 (bs, 2H) (Figure 3).

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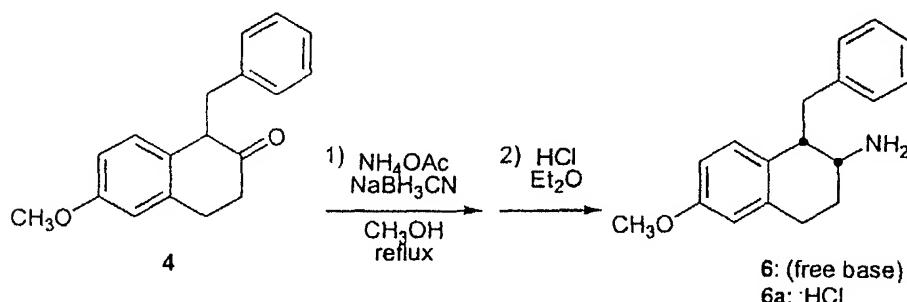


Figure 3

Alternatively, *cis*-1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenamine **6** is prepared as follows:

6-Methoxy-2-tetralone **1** (2.0 g, 11.3 mmol) was dissolved in benzene (60 mL) in a 100 mL round-bottom flask with stirring. N,N-dibenzylamine (2.4 mL, 12.5 mmol) was added and the flask was flushed with argon. A Dean-Stark trap and a condenser were attached and the solution was heated at reflux for 19 hours. After cooling, the solvents were removed *in vacuo* to afford enamine **7** which was used without further purification. MS (MH⁺) 356.

Enamine 7 was dissolved in acetonitrile (60 mL) in a 100 mL round-bottom flask and benzyl bromide (1.5 mL, 12.6 mmol) was added. The flask was flushed with argon and a reflux condenser was attached. The solution was heated at reflux for 14 hours. After cooling, the solvents were removed *in*

vacuo to yield iminium salt **8** as a glassy orange solid which was used without further purification. MS (MH⁺) 446.

Approximately half of the iminium salt from the previous reaction was transferred to a 250 mL Parr Shaker bottle along with methanol (50 mL). Separately, 10% palladium hydroxide on carbon (0.30 g) was placed into a vial and methanol (50 mL) was added carefully to form a slurry. This material was added to the iminium salt solution and the mixture was hydrogenated under a pressure of approximately 50 p.s.i. for 17 hours. The reaction solution was filtered over a pad of Celite to remove the catalyst. The solvent was removed *in vacuo*. The resulting oil was dissolved in ethyl acetate (300 mL) and this solution was washed with 0.2 M sodium hydroxide solution (2 x 125 mL) and then with water (1 x 100 mL). The aqueous layers were back extracted with ethyl acetate (1 x 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvents were removed *in vacuo*. The resulting oil was purified via chromatography (silica gel column (dimensions 5 x 28 cm) eluting first with dichloromethane (400 mL) and then with dichloromethane / acetone / methanol (50:50:5) (v/v). After evaporation of the appropriate fractions, *cis*-1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenamine **6** was obtained as a brown oil (0.37 g, 1.4 mmol). MS (MH⁺) 268; ¹H NMR (CDCl₃) δ 1.45 (bs, 2H), 1.86 (m, 2H), 2.80-3.07 (m, 5H), 3.20 (m, 1H), 3.75 (s, 3H), 6.52-6.67 (m, 3H), 7.10-7.30 (m, 5H). (Figure 4).

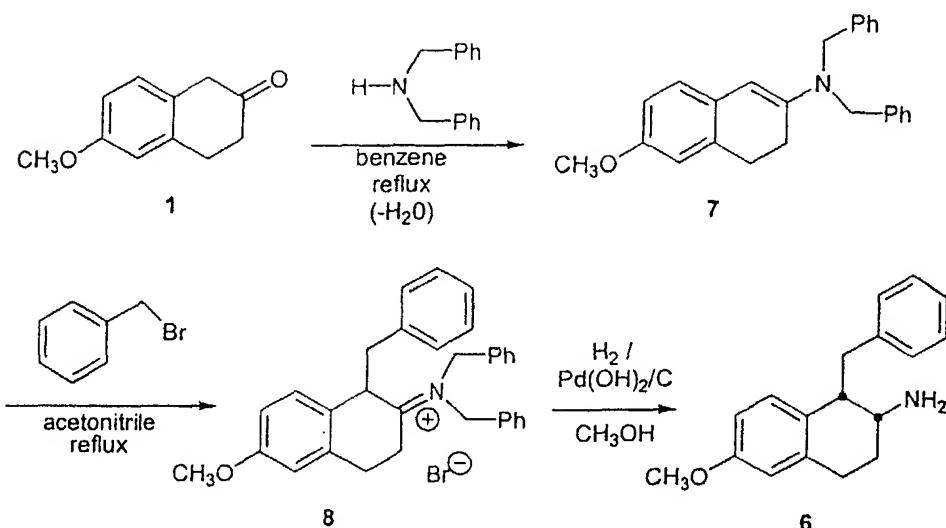


Figure 4

E. *trans*-4-(2-Naphthylsulfonamido)methylcyclohexanecarboxylic acid (0.394 g, 1.13 mmol) was placed in a 50 mL round-bottom flask and suspended in dichloromethane (10 mL). Triethylamine (0.32 mL, 2.3 mmol) was added which resulted in dissolution. Isobutylchloroformate (0.29 mL, 2.3 mmol) was slowly added and the mixture was stirred for 1 hour, presumably forming the anhydride species. *cis*-1,2,3,4-Tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenamine **6** (0.364 g, 1.36 mmol) was dissolved in dichloromethane (10 mL) and this solution was added to the solution prepared above. The reaction mixture was stirred for 3 hours at ambient temperature at which time an additional dichloromethane (50 mL) was added. This mixture was washed with 0.25 M sodium hydroxide solution (35 mL). The organic layer was separated and the aqueous layer was extracted with additional dichloromethane (2 x 25 mL). The organic extracts were combined and washed with brine (1 x 25 mL). The organics were dried over magnesium sulfate, filtered, and the solvents were removed *in vacuo*. The residue obtained was purified via chromatography (silica gel column (dimensions 2.5 x 26 cm) eluting with a gradient of: 100% dichloromethane (100 mL), 98:2 dichloromethane / acetone (100 mL), 96:4 dichloromethane / acetone (100 mL), 94:6 dichloromethane / acetone (100 mL), 92:8 dichloromethane / acetone (100 mL), then the remainder with 90:10 dichloromethane / acetone).

(100 mL). After evaporation of the appropriate fractions, [1 α ,2 α (*trans*)]-4-[(2-naphthalenylsulfonyl)amino]methyl]-N-[1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenyl]-cyclohexanecarboxamide **9** (0.314 g, 0.526 mmol) was obtained as an off-white powder. MS (MH $^+$) 597; 1 H NMR (DMSO-d₆) δ 0.71-0.85 (m, 2H), 1.25-1.38 (m, 3H), 1.69 (m, 5H), 1.90 (m, 1H), 2.10 (m, 1H), 2.43-2.63 (m, 3H), 2.79-2.96 (m, 3H), 3.11 (s, 1H), 3.65 (s, 3H), 3.82-3.92 (m, 1H), 6.31 (d, 1H), 6.45 (dd, 1H), 6.63 (d, 1H), 6.97 (app d, 2H), 7.13-7.26 (m, 3H), 7.68 (m, 3H), 7.85 (app d, 2H), 8.05 (app d, 1H), 8.15 (m, 2H), 8.44 (s, 1H).

10

F. The amide **9** from the previous reaction (0.282 g, 0.473 mmol) was suspended in tetrahydrofuran (20 mL) in a 50 mL round-bottom flask and lithium aluminum hydride solution (1.4 mL of a 1 M solution in THF) was added. The flask was flushed with argon and a condenser was attached. The reaction mixture was heated at reflux and during the course of the reaction more LAH solution was added (2.5 mL) and more THF was added (20 mL). After a reflux period of 50 hours, the reaction was cooled to room temperature and excess ethyl acetate was added to quench the remaining LAH. The solution was filtered over Celite to remove the inorganic salts. The solvents were removed *in vacuo*. The crude product was dissolved in ethyl acetate (150 mL) and washed with 1 M hydrochloric acid (2 x 50 mL). The organic extract was dried over magnesium sulfate, filtered, and the solvents were removed *in vacuo*. Excess ethereal hydrogen chloride (approx. 15 mL of a 1 M solution) was added and the solvents and excess HCl were removed *in vacuo*.

15 The product was recrystallized from ethyl acetate (15 mL) / acetone (19 mL) to yield [1 α ,2 α (*trans*)]-N-[[[1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl)methyl]-2-naphthalenesulfonamide hydrochloride **10a** (0.082 g, 0.132 mmol) as a white powder. MS (MH $^+$) 583; 1 H NMR (DMSO-d₆) δ 0.82-1.07 (m, 4H), 1.39 (m, 1H), 1.64-1.96 (m, 5H), 2.17 (m, 2H), 2.45 (m, 1H), 2.65 (m, 2H), 2.83-3.12 (m, 6H), 3.47 (m, 1H), 3.64 (s, 3H), 5.84 (d, 1H), 6.31 (d, 1H), 6.68 (app s, 1H), 7.06 (m, 2H), 7.27 (m, 4H), 7.70 (m, 2H), 7.83 (app d, 1H), 8.05 (app d, 1H), 8.16 (m, 2H), 8.43 (s, 1H), 8.95 (bs, 2H). (Figure 5).

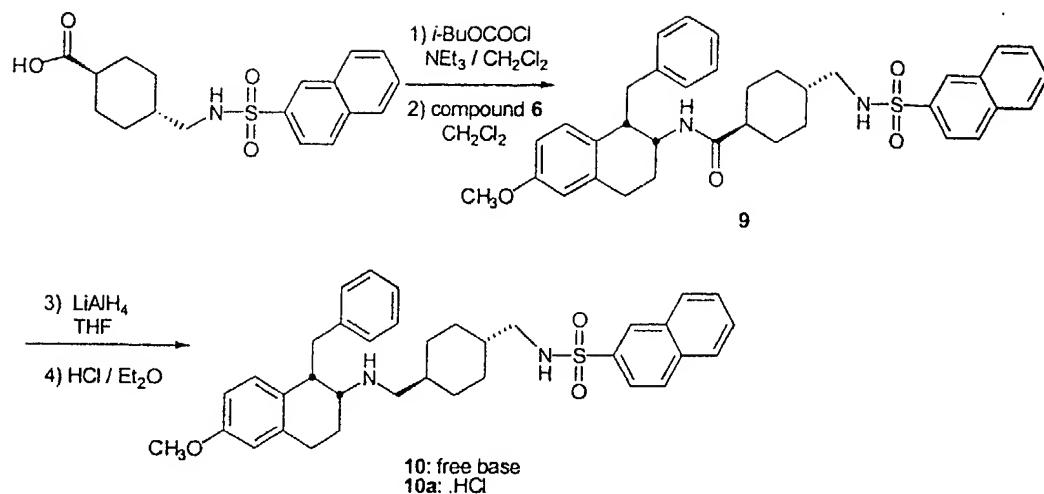


Figure 5

5

EXAMPLE 2

rac-[1*α*,2*α*(*trans*)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenyl]amino]-5-pentyl] 2-naphthalenesulfonamide (11)

10

3,4-Dihydro-6-methoxy-1-(phenylmethyl)-2(1H)-naphthalenone 4 (0.136 g, 0.511 mmol) was dissolved in methanol (5 mL) in a 20 mL screw cap vial equipped with a stir bar. After dissolution, 1-amino-5-(2-naphthalenylsulfonamido)pentane hydrochloride salt (0.170 g, 0.517 mmol) was added followed by sodium cyanoborohydride (0.098 g, 1.60 mmol). The vial was flushed with nitrogen and capped. Stirring was continued for 17 hours after which time dichloromethane (25 mL) and saturated sodium bicarbonate (25 mL) was added. The organics were removed and the aqueous layer was extracted with dichloromethane (2 x 25 mL). The organic extracts were combined and washed with brine (1 x 25 mL), dried over magnesium sulfate, filtered, and the solvents were removed *in vacuo*. The crude product was purified via chromatography (silica gel column (dimensions 2.5 x 17 cm); 25 % dichloromethane:75 % acetone (v/v) as the eluent). After evaporation of the appropriate fractions, the product was dissolved in ethyl ether and 1 M

hydrogen chloride in ethyl ether was added to precipitate [$1\alpha,2\alpha(\text{trans})$]-*N*-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenyl]amino]-5-pentyl] 2-naphthalenesulfonamide hydrochloride 11a (0.036 g, 0.062 mmol) as an off-white powder. MS (MH⁺) 543. (Figure 7)

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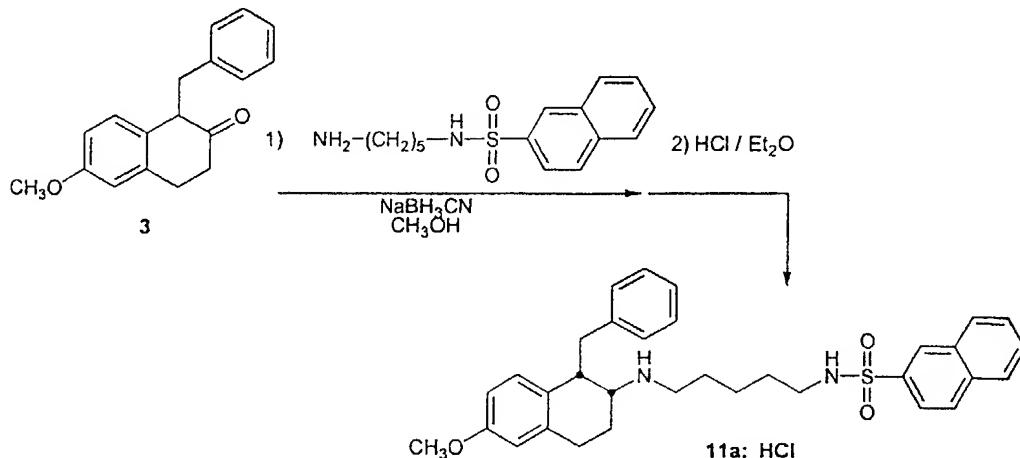


Figure 7

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EXAMPLE 3

rac-[$1\alpha,2\alpha(\text{trans})$]-*N*-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(3-pyridinylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] 2-naphthalenesulfonamide (18)

15

A. 6-Methoxy-β-tetralone 1 (2.0 g, 11.3 mmol) and diisopropylethylamine (0.20 mL, 1.1 mmol) were dissolved in benzene (60 mL) with stirring in a 100 mL round-bottom flask. 3-Pyridylcarboxaldehyde (1.1 mL, 11.7 mmol) was added and the reaction vessel was flushed with argon and a Dean-Stark trap with reflux condenser was attached. The mixture was heated at reflux for 19 hours. After cooling, HPLC analysis indicated that no products had formed. Piperidine (0.094 mL, 1.1 mmol) was added at this time and heating at reflux was continued for 23 hours. The solvents were removed *in vacuo* to yield a glassy orange solid. Chromatographic purification (silica gel column dimensions 5 x 29 cm) eluting with a gradient of: 100% hexane (400 mL),

20

25 (dimensions 5 x 29 cm) eluting with a gradient of: 100% hexane (400 mL),

75%/25% hexane/ethyl acetate (v/v) (400 mL), 50%/50% hexane/ethyl acetate (v/v) (400 mL), 25%/75% hexane/ethyl acetate (v/v) (400 mL), and finally with 100% ethyl acetate) was performed. After evaporation of the appropriate fractions, 3,4-dihydro-6-methoxy-1-((3-pyridinyl)methylidenyl)-2-naphthalenone

5 **12** (1.484 g, 5.59 mmol) was obtained as a orange oil which solidified upon standing in the refrigerator. MS (MH⁺) 266; ¹H NMR (CDCl₃) δ 2.67 (t, 2H), 3.02 (t, 2H), 3.83 (s, 3H), 6.60 (dd, 1H), 6.82 (d, 1H), 7.19 (m, 2H), 7.51 (s, 1H), 7.71 (d, 1H), 8.49 (dd, 1H), 8.65 (d, 1H).

10 B. The naphthalen-2-one **12** (1.442 g, 5.44 mmol) obtained above was dissolved in absolute ethanol (50 mL) and transferred to a 250 mL Parr hydrogenation bottle. Separately, ethanol was carefully added to 10% palladium on carbon (0.020g) and this slurry was added to the Parr bottle. The mixture was hydrogenated under a pressure of 50 psi for 16 hours. The catalyst was removed by filtration over Celite. Spectroscopic evidence indicated the presence of some starting material and so more palladium catalyst (0.081 g) was added to the ethanol solution and the hydrogenation was repeated for 20 hours. The catalyst was then removed by filtration over Celite. Removal of the solvents *in vacuo* yielded 3,4-dihydro-6-methoxy-1-(3-pyridinylmethyl)-2(1H)-naphthalenone **13** as an orange oil which was used in the next step without further purification. MS (MH⁺) 268.

C. Naphthalen-2-one **13** obtained above was dissolved in methanol (275 mL) in a 1 L round-bottom flask. Ammonium acetate (4.27 g, 55.4 mmol) was added to the stirred methanol solution and was allowed to completely dissolve before proceeding. Sodium cyanoborohydride (1.703 g, 27.5 mmol) was then added to the methanol solution. The reaction vessel was flushed with nitrogen and the solution refluxed for 18 hours. The solvents were then removed *in vacuo* to yield a yellow solid which was dissolved in ethyl ether (500 mL) and 0.1 M sodium hydroxide solution (275 mL). The organic layer was removed and washed with an additional 0.1 M sodium hydroxide solution (275 mL) and with water (250 mL). The combined aqueous washes were back extracted with ethyl ether (3 x 100 mL). The organic extracts were combined and dried

over sodium sulfate. The solvents were removed *in vacuo* and the residue was taken up in ethyl ether and a minimum amount of dichloromethane. An excess of 1 M hydrogen chloride in ethyl ether was added and a dark tan precipitate formed. The solvents were removed *in vacuo* and the resulting solid was titurated with ether and dried in a vacuum oven to yield 1,2,3,4-tetrahydro-6-methoxy-1-(3-pyridinylmethyl)-2-naphthalenamine bis-hydrochloride 14 as a tan-orange solid (1.208 g, 3.54 mmol) MS (MH⁺) 269; ¹H NMR (DMSO-d₆) δ 1.95-2.20 (m, 2H), 2.68-3.29 (m, 4H), 3.30-3.48 (m, 2H), 3.69 (s, 3H), 5.98 (d, 1H), 6.41 (dd, 1H), 6.75 (d, 1H), 7.98 (dd, 1H), 8.36 (d, 1H), 8.68-8.89 (m, 5H).

D. The 2-naphthalenamine 14 (1.193 g, 3.50 mmol) was dissolved in N,N-dimethylformamide (30 mL) in a 100 mL round-bottom flask and diisopropylethylamine (2.0 mL, 11.5 mmol) was added to the solution. N-(*tert*-Butoxycarbonyl)aminomethylcyclohexane carboxylic acid (0.912 g, 3.54 mmol) was added followed by HBTU (1.336 g, 3.52 mmol). The reaction mixture was stirred for 2 hours and then poured into water (400 mL). A fine precipitate formed which was separated by centrifugation followed by decanting, adding fresh water and re-centrifugation followed by a final decanting. The remaining material was dried in a vacuum oven and then purified via chromatography (silica gel column (5 x 17 cm) eluting with a gradient of: 75% hexane/ethyl acetate (v/v) (300 mL), 50% hexane/ethyl acetate (300 mL), 25% hexane/ethyl acetate (300 mL), and finally with 100% ethyl acetate. After evaporation of the appropriate fractions the resulting yellow solid was titurated with ethyl ether and then dried in a vacuum oven to yield [1 α ,2 α (*trans*)]-4-[(*tert*-butoxycarbonyl)amino]methyl]-N-[1,2,3,4-tetrahydro-6-methoxy-1-(3-pyridinylmethyl)-2-naphthalenyl]-cyclohexanecarboxamide 15 (0.629 g, 1.24 mmol) MS (MH⁺) 508; ¹H NMR (DMSO-d₆) δ 0.81-1.04 (m, 2H), 1.31-1.54 (m, 13H), 1.70-2.02 (m, 7H), 2.80-3.04 (m, 6H), 3.35 (m, 1H), 3.79 (s, 3H), 4.27 (m, 1H), 4.59 (m, 1H), 5.42 (d, 1H), 6.58-6.77 (m, 3H), 7.47 (d, 1H), 8.34 (s, 1H), 8.48 (d, 1H).

- E. The carboxamide **15** obtained above (0.603 g, 1.19 mmol) was suspended in 100 mL dioxane in a 250 mL round-bottom flask. While cooling with an ice bath, hydrogen chloride gas was bubbled into the solution until saturated. The solvents were removed *in vacuo* and the resulting material was dissolved in methanol and an excess of ethereal hydrogen chloride was added. The solvents were removed *in vacuo* and the resulting product was titrated with ethyl ether and filtered. The resultant hygroscopic off-white solid was dried at 40°C in a vacuum oven to afford [1 α ,2 α (*trans*)]-4-(aminomethyl)-N-[1,2,3,4-tetrahydro-6-methoxy-1-(3-pyridinylmethyl)-2-naphthalenyl]-cyclohexanecarboxamide bis-hydrochloride **16** (0.502 g, 1.04 mmol). MS (MH $^+$) 408; 1 H NMR (DMSO-d₆) δ 0.80-1.03 (m, 2H), 1.19-1.42 (m, 2H), 1.44-1.89 (m, 6H), 1.93 (m, 1H), 2.10 (m, 1H), 2.56-2.70 (m, 2H), 2.71-3.01 (m, 3H), 3.09 (m, 1H), 3.34 (m, 1H), 3.70 (s, 3H), 3.91 (m, 1H), 6.58-6.63 (m, 2H), 6.71 (s, 1H), 7.87-8.11 (m, 5H), 8.22 (d, 1H), 8.59 (s, 1H), 8.75 (d, 1H).
- F. The amine hydrochloride **16** obtained above (0.102 g, 0.212 mmol) was mixed with dichloromethane (13 mL) and diisopropylethylamine (0.125 mL, 0.718 mmol). 2-Naphthylsulfonylchloride (0.048 g, 0.212 mmol), dissolved in dichloromethane (12 mL), was added to the mixture. The resulting solution was stirred for 1 hour after which the solvents were removed *in vacuo*. The residue was taken up in dichloromethane (75 mL) and this mixture was washed with 0.1 M sodium hydroxide solution (2 x 55 mL) and water (1 x 50 mL). The organics were dried over magnesium sulfate and the solvents were removed *in vacuo* to yield [1 α ,2 α (*trans*)]-4-[(2-naphthalenylsulfonyl)amino]methyl]-N-[1,2,3,4-tetrahydro-6-methoxy-1-(3-pyridinylmethyl)-2-naphthalenyl]-cyclohexanecarboxamide **17** (0.126 g, 0.211 mmol). MS (MH $^+$) 598.

- G. The carboxamide **17** obtained above (0.119 g, 0.199 mmol) was dissolved in tetrahydrofuran (15 mL) in a 100 mL round-bottom flask. Borane-tetrahydrofuran (2.00 mL of a 1 M solution, 2.00 mmol) was added. The resultant mixture was stirred for 3 hours at room temperature at which time it was found that the reaction was proceeding very slowly (HPLC). A reflux

condenser was attached and the solution was heated at reflux for 1 hour. After the solution had cooled, water (2 mL) was added to quench the excess borane. The solvents were then removed *in vacuo*. Hydrochloric acid (15 mL of a 6 M solution) was added to the residue and this mixture was heated at reflux for 30 minutes. The solution was cooled and dichloromethane (100 mL) and 1 M sodium hydroxide solution (100 mL) were added. The organic extract was removed and the aqueous layer was washed with dichloromethane (2 x 100 mL). The organic extracts were combined and dried over magnesium sulfate and the solvents were removed *in vacuo*. Ethyl ether (100 mL) was added along with enough methanol to solubilize the free base. An excess of ethereal hydrogen chloride was added and the solvents were removed *in vacuo*. The product was titurated with ethyl ether and dried in a vacuum oven to yield [1 α ,2 α (*trans*)]-*N*-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(3-pyridinylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl]-2-naphthalenesulfonamide bis-hydrochloride **18a** (0.110 g, 0.167 mmol). MS (MH $^+$) 584; 1 H NMR (DMSO-d₆) δ 0.70-1.03 (m, 4H), 1.19-1.44 (m, 2H), 1.65-1.87 (m, 3H), 1.88-2.02 (m, 2H), 2.07-2.30 (m, 2H), 2.64 (dd, 2H), 2.69-3.19 (m, 4H), 3.33-3.62 (m, 3H), 3.65 (s, 3H), 5.82 (d, 1H), 6.35 (dd, 1H), 6.72 (dd, 1H), 7.63-7.88 (m, 4H), 7.93 (dd, 1H), 8.05 (d, 1H), 8.16 (m, 2H), 8.30 (d, 1H), 8.42 (s, 1H), 8.71 (s, 1H), 8.75 (d, 1H), 9.08 (br, 1H), 9.53 (br, 1H) (Figure 8).

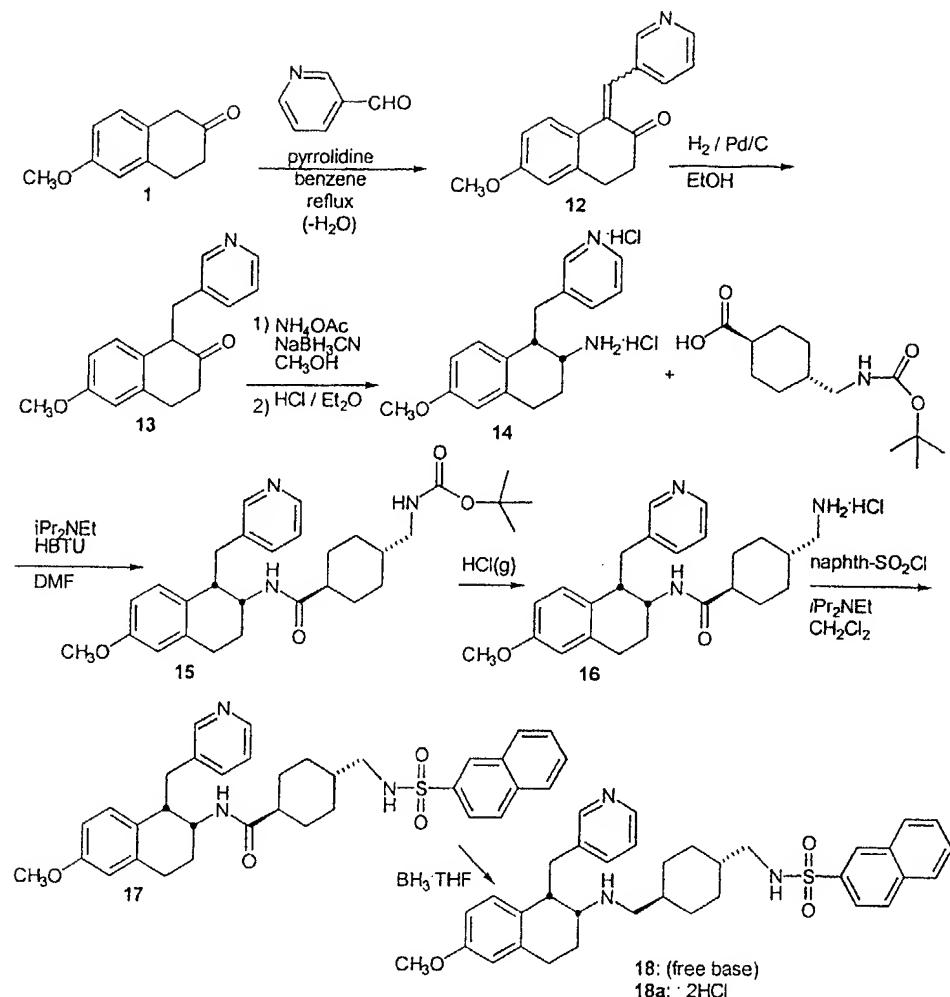


Figure 8

EXAMPLE 4

5

rac-[1 α ,2 α (trans)]-N-[[[[[1,2,3,4-tetrahydro-6-fluoro-1-(3-phenylmethyl)-2-naphthalenyl]amino)methyl]-4-cyclohexyl]methyl] 2-fluorobenzenesulfonamide

(26)

10

A. 3,4-Dihydro-6-fluoro-2(1H)-naphthalenone was prepared using a modified procedure of Stjernlof, P.; et. al. (*J. Med. Chem.* 1995, 38, 2202). A solution of 4-fluorophenylacetic acid (10.0 g, 64.9 mmol) and thionyl chloride (11.8 mL, 0.162 mol) in 1,2-dichloroethane (150 mL) was heated at reflux for 4

h, in a 500 mL round-bottom flask. The solvent was evaporated *in vacuo*. The residue was dissolved in 1,2-dichloroethane and the solvent evaporated *in vacuo* (in order to remove excess thionyl chloride). The residue was dissolved in dichloromethane (50 mL) and the solution was added dropwise, over 20 min,

5 to a cooled suspension of aluminum chloride (21.6 g, 162 mmol) in dichloromethane (250 mL) at -10 to -5°C. The suspension was stirred at -10°C for 10 min. Ethylene was bubbled rapidly through the suspension for 20 min at -10 to 5°C. Bubbling was continued at a very slow rate for the next 2 h while maintaining a temperature of -5°C. The reaction mixture was quenched with

10 ice (100 g), and the organic layer was separated and washed twice with water and once with a saturated aqueous sodium bicarbonate solution. The organic solution was dried over magnesium sulfate and the solvent was evaporated *in vacuo* to give the crude tetralone (13.2 g), as a yellow solid. The tetralone was used without purification in the subsequent reaction although a portion of the

15 crude product was recrystallized from hexanes to give purified 3,4-dihydro-6-fluoro-2(1H)-naphthalenone as a colorless solid (~50% recovery). ¹H NMR (CDCl₃) δ 2.55 (t, 2H), 3.05 (t, 2H), 3.54 (s, 2H), 6.85-6.97 (m, 2H) and 7.05-7.12 (m, 1H).

20 B. Pyrrolidine (1.78 mL, 21.4 mmol) was added to a solution 3,4-dihydro-6-fluoro-2(1H)-naphthalenone (3.2 g, 19.5 mmol) in benzene (40 mL) in a 100 mL round-bottom flask and the resultant solution was stirred at room temperature for 1 h. The solvent was evaporated *in vacuo*. The residue was dissolved in 1,2-dichloroethane and the solvent was evaporated *in vacuo* (to remove excess pyrrolidine). The crude product, 6-fluoro-2-(pyrrolidin-1-yl)-3,4-dihydropnaphthalene **19** was used without purification in the subsequent step.

25 C. Benzyl bromide (2.8 mL, 23.4 mmol) was added to a solution of the crude enamine **19** (19.5 mmol) in acetonitrile (60 mL) in a 100 mL round-bottom flask and the resultant solution was stirred at room temperature for 1.5 h. The solvent was evaporated *in vacuo* and the residue was crystallized from hot tetrahydrofuran. The suspension was cooled and the iminium salt **20** was collected by filtration to give a white solid, 4.4 g (58%). MS m/e (M⁺) 308. ¹H

NMR (DMSO-d₆): δ 1.70-2.03 (m, 4H), 2.91-3.13 (m, 3H), 3.17-3.29 (m, 2H), 3.38-3.61 (m, 2H), 3.81-3.93 (m, 1H), 3.96-4.07 (m, 1H), 4.13-4.27 (m, 1H), 4.52 (t, 1H), 6.87-7.02 (m, 2H), 7.09-7.17 (m, 2H) and 7.20-7.32 (m, 2H).

5 D. The iminium salt **20** (4.4 g, 11.33 mmol) was mixed with acetic acid (5 mL, 87.3 mmol), dichloromethane (50 mL), water (50 mL) and methanol (100 mL) in a 500 mL round-bottom flask, and stirred at room temperature for 16 h. An organic layer formed and was separated and the aqueous layer was extracted with dichloromethane. The organic extracts were combined, washed
10 twice with water and once with a saturated solution of aqueous sodium bicarbonate, and then dried over magnesium sulfate. The solvent was evaporated *in vacuo* to give 3,4-dihydro-6-fluoro-1-(phenylmethyl)-2(1H)-naphthalenone **21** as a tan oil, 3.0 g (100%). This material was used without further purification in the subsequent step.

15

E. A solution of 3,4-dihydro-6-fluoro-1-(phenylmethyl)-2(1H)-naphthalenone **21** from above (2.9 g, 11.4 mmol) was dissolved in methanol (50 mL) in a 250 mL round-bottom flask. Ammonium acetate (13.2 g, 0.171 mol) was added and the mixture was stirred at room temperature for 10 min. Sodium
20 cyanoborohydride (3.58 g, 57 mmol) was added and the resultant solution was heated at reflux for 1 h. The solvent was evaporated *in vacuo*, and the residue was treated with aqueous sodium hydroxide (50 mL of a 1 N solution). The product was extracted into dichloromethane (2 x 50 mL) and washed twice with water and dried over sodium sulfate. The solvent was evaporated *in vacuo*, and the residue was dissolved in diethyl ether (50 mL) and treated with
25 ethereal hydrochloric acid (15 mL of a 1 N solution) which resulted in the precipitation of a solid. This material was collected by filtration, washed with diethyl ether and dried *in vacuo* to give *cis*-1,2,3,4-tetrahydro-6-fluoro-1-(phenylmethyl)-2-naphthalenamine hydrochloride **22** as a pale pink solid (1.6 g, 48%). MS m/e (MH⁺) 256. ¹H NMR (DMSO-d₆): δ 1.96-2.13 (m, 2H), 2.40 (t, 1H), 2.82-3.12 (m, 2H), 3.17 (dd, 1H), 3.28-3.37 (m, 1H), 3.47-3.60 (br m, 1H), 5.98 (m, 1H), 6.62 (m, 1H), 6.98 (m, 1H), 7.08 (d, 2H), 7.18-7.30 (m, 3H), 8.64 (br s, 3H).

F. *cis*-1,2,3,4-Tetrahydro-6-fluoro-1-(phenylmethyl)-2-naphthalenamine hydrochloride **22** (0.96 g, 3.29 mmol) was dissolved in N,N-dimethylformamide (50 mL) in a 250 mL round-bottom flask with stirring. Diisopropylethylamine 5 (1.30 mL, 7.46 mmol) was added followed by 4-(*tert*-butoxycarbonyl)aminomethylcyclohexane carboxylic acid (0.85 g, 3.31 mmol). To this stirred solution, HBTU (1.25 g, 3.29 mmol) was added slowly. The flask was flushed with argon, capped, and allowed to stir for 3 hours. At this time the reaction solution was poured into 500 mL water. A precipitate immediately 10 formed and this slurry was stirred overnight. The solid was then filtered and rinsed with additional portions of water. Air was pulled over the solid until nearly dry. This solid was added to methanol (15 mL) and the solid-liquid mixture was heated to reflux for several minutes. After cooling the solution to room temperature, the white solid was filtered away from the orange-brown 15 liquid. The filtrate was evaporated slightly to provide a second batch of white solid which was filtered as before and combined with the first batch. This white solid was dried *in vacuo* to afford [1 α ,2 α (*trans*)]-4-[(*tert*-butoxycarbonyl)amino]methyl]-N-[1,2,3,4-tetrahydro-6-fluoro-1-(3-phenylmethyl)-2-naphthalenyl]-cyclohexanecarboxamide **23** (1.28 g, 2.59 20 mmol). MS m/e (MH $^+$) 256. 1 H NMR(CDCl $_3$): δ 0.79-1.00 (m, 2H), 1.23-1.53 (m, 12H), 1.70-2.08 (m, 7H), 2.75-3.03 (m, 6H), 3.37 (m, 1H), 4.29 (m, 1H), 4.55 (m, 1H), 5.33 (d, 1H), 6.67-6.87 (m, 3H), 7.12 (d, 2H), 7.37-7.18 (m, 3H).

G. The carboxamide **23** obtained above (1.28 g, 2.58 mmol) was dissolved 25 in dioxane (150 mL) in a 250 mL round-bottom flask and cooled in an ice bath. Excess gaseous hydrogen chloride was added to the resultant solid-liquid mixture until saturation. The clear solution was then warmed to room temperature and stirred until the starting material was completely consumed (HPLC). The solvents were removed *in vacuo* and the resulting solid titurated 30 with diethyl ether to yield a white solid which upon filtration and drying *in vacuo* afforded [1 α ,2 α (*trans*)]-4-(aminomethyl)-N-[1,2,3,4-tetrahydro-6-fluoro-1-(phenylmethyl)-2-naphthalenyl]-cyclohexanecarboxamide hydrochloride **24**. MS m/e (MH $^+$) 395; 1 H NMR (DMSO-d $_6$): δ 0.84-1.05 (m, 2H), 1.28-1.49 (m, 2H),

1.50-1.62 (m, 1H), 1.65-2.04 (m, 6H), 2.09-2.27 (m, 1H), 2.51-2.59 (m, 1H),
2.60-2.73 (m, 2H), 2.77-3.04 (m, 3H), 3.12-3.26 (m, 1H), 3.92 (m, 1H), 6.41
(dd, 1H), 6.73 (dt, 1H), 6.89-7.05 (m, 3H), 7.13-7.32 (m, 3H), 7.88 (br, 3H),
7.97 (d, 1H).

5

H. The naphthalenyl carboxamide **24** (0.087 g, 0.20 mmol) was dissolved in a dichloromethane solution (15 mL) of diisopropylethylamine (0.080 mL, 0.46 mmol) with stirring, in 100 mL round-bottom flask. A solution of 2-fluorobenzenesulfonyl chloride (0.045 g, 0.23 mmol) in dichloromethane (15 mL) was added. The reaction mixture was allowed to stir overnight at room temperature. The solvent was removed *in vacuo* to give a glassy colorless material. This material was dissolved in dichloromethane (100 mL) and the solution was washed with 0.1 M sodium hydroxide solution (2 x 55 mL) and then with water (1 x 50 mL). The organics were dried over magnesium sulfate, filtered, and the solvents removed *in vacuo* to yield [1 α ,2 α (*trans*)]-4-[(2-fluorobenzenesulfonyl)amino]methyl]-N-[1,2,3,4-tetrahydro-6-fluoro-1-(phenylmethyl)-2-naphthalenyl]-cyclohexanecarboxamide **25** (0.110g, 0.199 mmol) as a tan powder. MS m/e (MH⁺) 553; ¹H NMR (DMSO-d₆): δ 0.71-0.91 (m, 2H), 1.18-1.43 (m, 3H), 1.61-1.81 (m, 5H), 1.85-2.00 (m, 1H), 2.03-2.19 (m, 1H), 2.51 (m, 1H, obscured by DMSO), 2.71 (t, 2H), 2.79-3.03 (m, 3H), 3.08-3.24 (m, 1H), 3.91 (m, 1H), 6.42 (dd, 1H), 6.72 (dt, 1H), 6.86-7.02 (m, 3H), 7.08-7.29 (m, 3H), 7.33-7.52 (m, 2H), 7.65-7.77 (m, 1H), 7.79 (dt, 1H), 7.84-7.99 (m, 2H).

I. The carboxamide **25** obtained above (0.110 g, 0.199 mmol) was dissolved in THF (15 mL) and with stirring, a solution of borane-tetrahydrofuran complex solution (1 M in THF, 2.0 mL, 2.0 mmol) was added. The solution was flushed with nitrogen and then heated at reflux for about 1 hour. After cooling to room temperature, water (2 mL) was added dropwise to the solution with stirring and the solvents were removed *in vacuo* to give a white film. Hydrochloric acid (15 mL of a 6 M solution) was added to this material and the mixture was heated at reflux for approximately 30 minutes. After cooling to room temperature sodium hydroxide (100 mL of a 1 N solution) was added.

This aqueous mixture was extracted with dichloromethane (3 x 100 mL). The organic extracts were combined and dried over magnesium sulfate, filtered, and the solvents were removed *in vacuo*. The residue was dissolved in THF (4 mL) and ethereal hydrogen chloride (2 mL of a 1 M solution) was added. The solvents were removed *in vacuo* to give a white gelatinous solid. Methanol and dichloromethane were added to break up the solid and then removed *in vacuo* to give a white powder. Isopropanol (4 mL) was added and the slurry was briefly heated at reflux then cooled. The solvent was removed and the moist product was dried under vacuum to afford [1 α ,2 α (*trans*)]-*N*-[[[[[1,2,3,4-tetrahydro-6-fluoro-1-(3-phenylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] 2-fluorobenzenesulfonamide **26** (0.087 g, 0.151 mmol) as a white powder. MS m/e (MH⁺) 539; ¹H NMR (DMSO-d₆): δ 0.71-1.03 (m, 4H), 1.24-1.43 (m, 1H), 1.61-1.97 (m, 5H), 2.03-2.25 (m, 2H), 2.44 (m, 1H), 2.73 (t, 2H), 2.83-3.18 (m, 5H), 3.40-3.59 (m, 2H), 5.96 (dd, 1H), 6.59 (dt, 1H), 6.98 (dd, 1H), 7.07 (d, 2H), 7.17-7.32 (m, 3H), 7.36-7.53 (m, 2H), 7.73 (q, 1H), 7.81 (dt, 1H), 7.98 (t, 1H), 8.85 (br, 2H) (Figure 9).

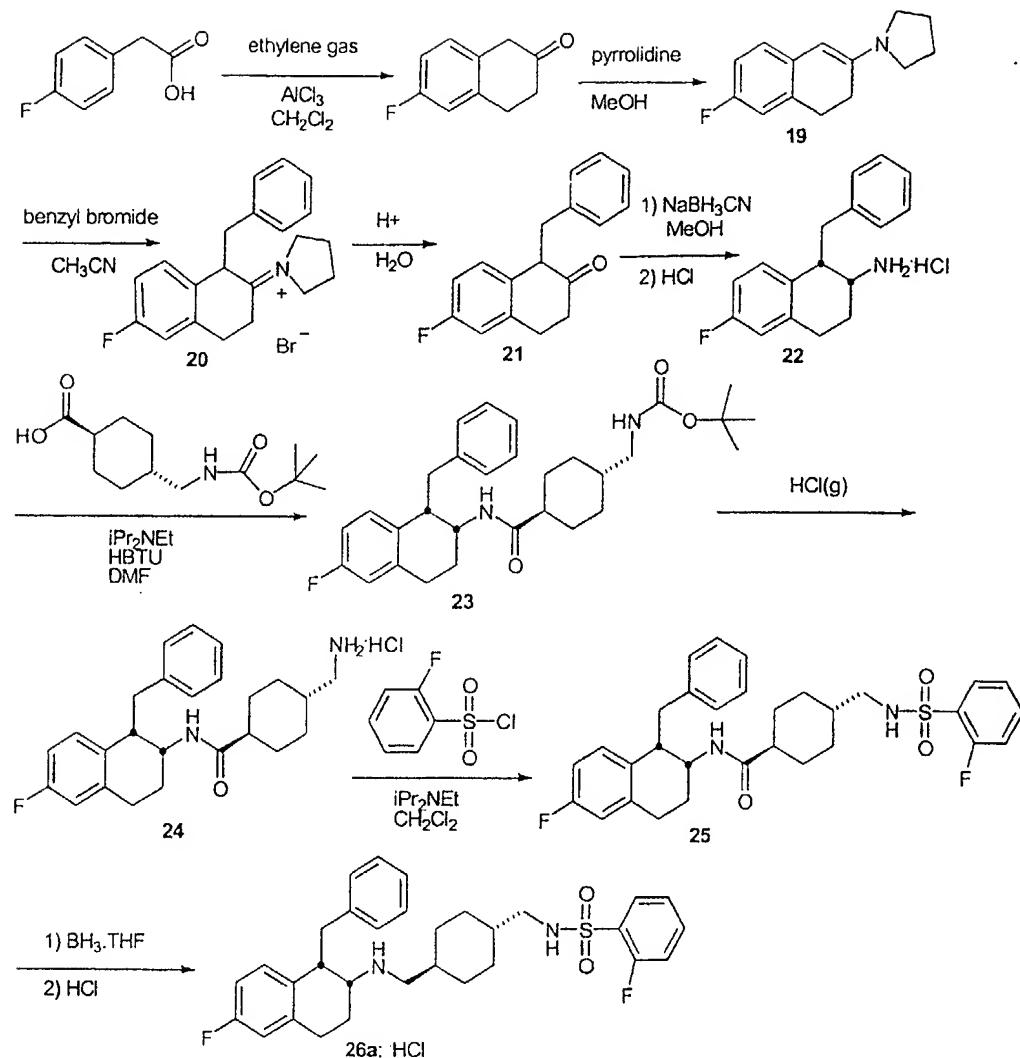


Figure 9

5

EXAMPLE 5

rac-[1 α ,2 α (*trans*)]-N-[[[[[1,2,3,4-tetrahydro-6-fluoro-1-phenyl-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl]naphthalenesulfonamide

2-

10 (34)

A. A solution of phenylmagnesium bromide in diethyl ether (3.0 M, 23 mL, 69 mmol) was added dropwise to a solution of 6-methoxy-1,2,3,4-

tetrahydronaphthalen-1-one **27** (10.0 g, 56.7 mmol) in diethyl ether (100 mL) at room temperature. The reaction mixture was heated at reflux for 1.5 h. An additional portion of phenylmagnesium bromide solution (10 mL, 60 mmol) was added to the cooled reaction mixture, and the resultant mixture was heated at 5 reflux for an additional 2.5 h. The cooled mixture was poured into a saturated solution of ammonium chloride (200 mL), and stirred for 15 min. The organic layer was separated, washed with a saturated solution of sodium chloride, and dried over magnesium sulfate. The solvent was evaporated *in vacuo*, and the resultant oil was treated with a solution of sulfuric acid (8mL) in acetic acid 10 (30mL) at room temperature for 1.5 h. Ice water (300 mL) was added to the solution, and the product was extracted into dichloromethane (200 mL), washed with water, and a saturated aqueous solution of sodium bicarbonate, and dried over magnesium sulfate. The solvent was evaporated *in vacuo* and the residue was purified by medium pressure chromatography using ethyl 15 acetate 0 to 3% in hexanes as the eluent, to give the 6-methoxy-1-phenyl-3,4-dihydronaphthalene **28** in two crops 4.0 g (29 %) and an impure fraction 5.02 g (37%) as an oil.

B. Borane in tetrahydrofuran (34 mL of a 1M solution, 34 mmol) was added 20 to tetrahydrofuran (50 mL) and the resultant solution was cooled to 0°C. A solution of 6-methoxy-1-phenyl-3,4-dihydronaphthalene **28** (5.0 g, 21.2 mmol) in tetrahydrofuran (10 mL) was added. The resultant mixture was stirred at ambient temperature for 18 h. A solution of water (5 mL) in tetrahydrofuran (20 mL) was slowly added to the cooled solution which resulted in considerable 25 foaming. Additional water (10 mL) was added followed by 10% aqueous sodium hydroxide (15 mL) and 30% hydrogen peroxide (30 mL). The resultant mixture was stirred at room temperature for 6 h. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic solutions were washed with a saturated aqueous 30 sodium chloride and dried over magnesium sulfate. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography using 30 to 40% ethyl acetate in hexanes as the eluent, to afford *trans*-6-methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-ol **29** as an oil (2.0 g, 37%).

¹H NMR(CDCl₃) δ 1.77 (d, 1H), 1.83-1.97 (m, 1H), 2.13-2.22 (m, 1H), 2.94-3.05 (m, 2H), 3.78 (s, 3H), 3.90 (d, 1H), 3.98-4.07 (m, 1H), 6.59-6.70 and 7.16-7.39 (m, 8H).

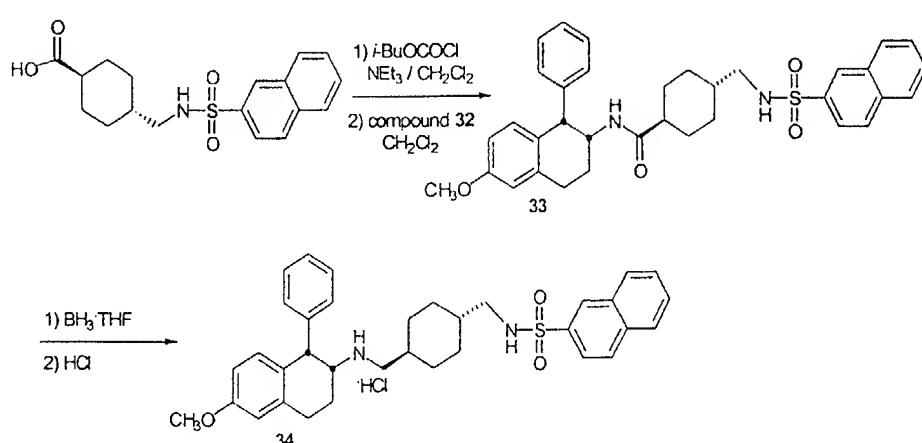
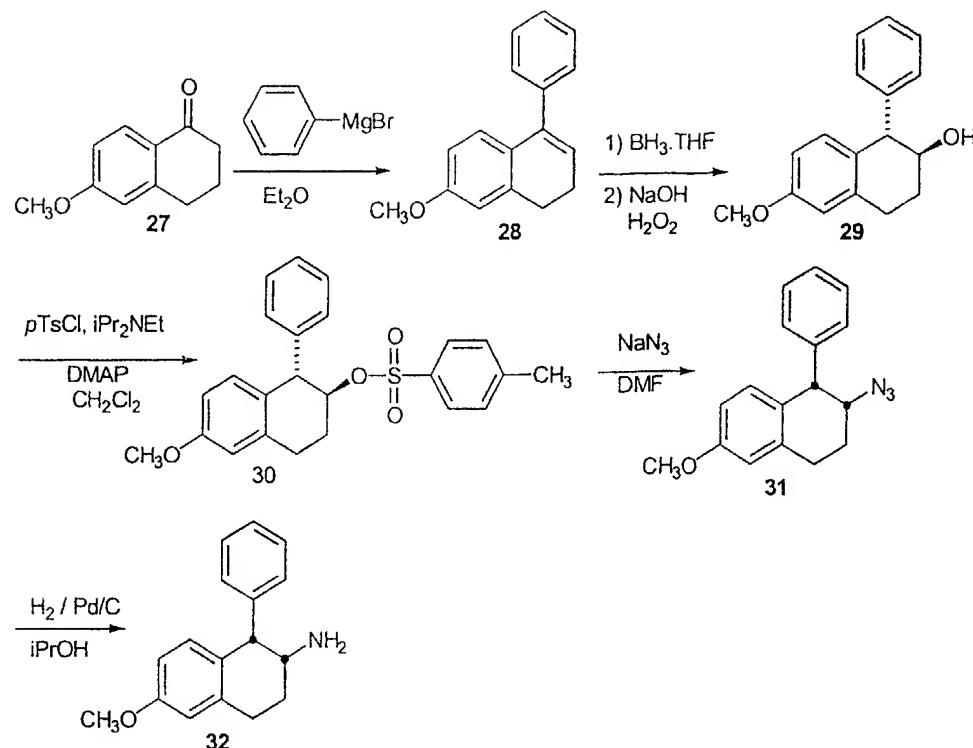
- 5 C. A solution of *para*-toluenesulfonyl chloride (1.8 g, 9.43 mmol) in dichloromethane (10 mL) was added to a solution of *trans*-6-methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-ol **29** (2.0 g, 7.86 mmol), *N,N*-diisopropylethylamine (4.8 mL, 27.5 mmol) and 4-dimethylaminopyridine (1.15 g, 9.43 mmol) in dichloromethane (40 mL) at 0°C. The resultant solution was
10 stirred at ambient temperature for 16 h. The solution was washed successively with 1 N aqueous sodium hydroxide (x 2) and a saturated aqueous solution of sodium chloride, then dried over sodium sulfate. The solvent was evaporated *in vacuo* to give crude *trans*-6-methoxy-1-phenyl-2-(4-methylbenzenesulfonyl)oxy-1,2,3,4-tetrahydronaphthalene **30** (3.47 g), as a
15 pale yellow solid which was used without further purification in the subsequent step. ¹H NMR(CDCl₃) δ 1.90-2.04 (m, 1H), 2.14-2.24 (m, 1H), 2.42 (s, 3H), 2.83-3.07 (m, 2H), 3.77 (s, 3H), 4.16 (d, 1H), 4.80-4.87 (m, 1H), 6.60-6.67 (m, 3H), 6.82-6.90 (m, 2H), 7.13-7.23 (m, 5H), 7.58 (d, 2H).
- 20 D. A *N,N*-dimethylformamide solution (50 mL) of crude *trans*-6-methoxy-1-phenyl-2-(4-methylbenzenesulfonyl)oxy-1,2,3,4-tetrahydronaphthalene **30** (3.4 g), sodium azide (3.78 g, 58.3 mmol) and 15-crown-5 (6.61 mL, 33.2 mmol) was heated at 75°C for 7 h. The reaction mixture was poured into ice water (200 mL), and the product was extracted into diethyl ether (3 x 50 mL). The
25 organic extracts were combined and washed successively with water (4 x 100 mL) and a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. The solvent was evaporated *in vacuo*, and the remaining residue was purified by medium pressure chromatography using 3 % ethyl acetate in hexanes as the eluent to give crude *cis*-2-azido-6-methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalene **31** (1.35 g, ~62 %) as an oil which was
30 used without further purification in the subsequent step.

E. The azido-tetrahydronaphthalene 31 obtained above (1.3 g) was dissolved in isopropanol (50 mL) and this solution was hydrogenated at 50 psi over 10% palladium on carbon (0.2 g) at room temperature for 18 h. The catalyst was removed by filtration and the solvent was evaporated *in vacuo* to afford crude *cis*-1,2,3,4-tetrahydro-6-methoxy-1-phenyl-2-naphthalenamine 32 as an oil, which was used in the subsequent step without purification (Figure 10). MS m/e (MH⁺) 254.

F. A solution of isobutylchloroformate (0.88 mL, 6.76 mmol) in dichloromethane (5 mL) was added dropwise to a solution of *trans*-4-(2-naphthylsulfonamido)methylcyclohexanecarboxylic acid (1.12 g, 3.22 mmol) and triethylamine (1.35 mL, 9.66 mmol) in dichloromethane (30 mL) at 0°C. The resultant solution was stirred at room temperature for 1 h. A solution of naphthalenamine 32 (4.65 mmol) in dichloromethane was added dropwise to the reaction mixture at 0°C. The reaction was stirred at ambient temperature for 16 h after which time, solvents and other volatile materials were evaporated *in vacuo*. The resultant residue was treated with a solution of 1N aqueous sodium hydroxide (20 mL) and tetrahydrofuran (20 mL) for 30 min. The solution was concentrated in *vacuo* and acidified with 1N aqueous hydrochloric acid (30 mL). The product was extracted into 10 % isopropanol in dichloromethane (2 x 50 mL). The solvent was evaporated *in vacuo* and the residue was purified by medium pressure chromatography using 2 % methanol in dichloromethane as the eluent, to give [1 α ,2 α (*trans*)]-4-[(2-naphthalenylsulfonyl)amino]methyl]-N-[1,2,3,4-tetrahydro-6-methoxy-1-phenyl-2-naphthalenyl]-cyclohexanecarboxamide 33 (0.95 g, 52%) as a glass, which was crystallized from diethyl ether to give a colorless solid (0.38 g, 20%). MS m/e (MH⁺) 583; ¹H NMR(DMSO-d₆) δ 0.68-0.83 (m, 2H), 1.20-1.37 (m, 3H), 1.50-1.77 (m, 6H), 1.87-1.99 (m, 1H), 2.60 (t, 2H), 2.90-3.02 (m, 2H), 3.73 (s, 3H), 3.94-4.07 (m, 1H), 4.40 (d, 1H), 6.61-6.81 (m, 5H), 7.14-7.32 (m, 4H), 7.63-7.75 (m, 3H), 7.81 (d, 1H), 8.04 (d, 1H), 8.14 (t, 2H) and 8.43 (s, 1H).

G. A 1 M solution of borane in tetrahydrofuran (5 mL, 5 mmol) was added dropwise to a solution of carboxamide 33 (0.25 g, 0.43 mmol) in

tetrahydrofuran (15 mL) and stirred at ambient temperature for 5 h. Water (5 mL) in tetrahydrofuran (15 mL) was added dropwise to the solution at 0°C over 10 min. Hydrochloric acid (5 mL of a 4 N solution) was added to the solution, and the resultant mixture was stirred at 0°C for 16 h. The reaction mixture was 5 concentrated *in vacuo*, and neutralized with aqueous sodium bicarbonate. The product was extracted into dichloromethane (2 x 50 mL). The organic extracts were combined and the solvent was evaporated *in vacuo*. The resultant residue was purified by preparative reverse phase HPLC using 0.1% trifluoroacetic acid in acetonitrile and water as the eluent. The product eluted 10 at 55% acetonitrile to afford the trifluoroacetic acid salt of [1 α ,2 α (*trans*)]-N-[[[[1,2,3,4-tetrahydro-6-methoxy-1-phenyl-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] 2-naphthalenesulfonamide **34** as a colorless solid (0.125 g, 43%). MS (MH⁺) 569; 1H NMR(DMSO-d₆) δ 0.73-0.90 (m, 4H), 1.23-1.36 (m, 1H), 1.40-1.57 (m, 1H), 1.60-1.75 (m, 4H), 1.83-2.09 (m, 2H), 2.60 (t, 2H, 15 collapses to d with D₂O), 2.64-2.77 (m, 1H), 2.87-3.16 (m, 3H), 3.62-3.76 (m, 1H), 3.73 (s, 3H), 4.58 (d, 1H), 6.68 (dd, 1H), 6.76-6.80 (m, 2H), 7.13 (d, 2H), 7.24-7.37 (m, 3H), 7.67-7.77 (m, 3H, collapses to 2H with D₂O), 7.83 (d, 1H), 7.87-8.00 (br s, 1H, exchanges with D₂O), 8.06 (d, 1H), 8.10-8.26 (m, 3H) and 8.43 (s, 1H). (Figure 11).



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EXAMPLE 6

- rac-[1 α ,2 α (trans)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(1-propene-3-yl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] benzenesulfonamide
 10 (39)

- A. 3,4-Dihydro-6-methoxy-2-(pyrrolidin-1-yl)naphthalene **2** was prepared by reacting a solution of 6-methoxy- β -tetralone (4.73 g, 26.8 mmol) in methanol (50 mL) with pyrrolidine (2.35 mL, 28.18 mmol) in a 100 mL round-bottom flask 5 at room temperature for 30 min. The solvent was evaporated *in vacuo* to afford the desired enamine **2** as a yellow solid (a single component by reverse phase HPLC), which was used without purification in the subsequent step.
- B. Enamine **2** (26.8 mmol) was dissolved in acetonitrile (50 mL) in 100 mL round-bottom flask and allyl bromide (2.55 mL, 29.5 mmol) was added. After stirring at room temperature for 18 h, the solvent was evaporated *in vacuo* and the resultant residue was titrated with tetrahydrofuran. The corresponding iminium salt **35** was collected by filtration as a gummy solid and used without further purification in the subsequent step. The product is a single component 15 by reverse phase HPLC. MS (M⁺) 270. ¹H NMR (CDCl₃): δ 2.00-2.15 (m, 4H), 2.33-2.47 (m, 1H), 2.60-2.70 (m, 1H), 2.90-3.34 (m, 2H), 2.90-3.34 (m, 4H), 3.76 (m, 3H), 3.84-4.16 (m, 3H), 4.23-4.39 (m, 2H), 5.04 (d, 1H), 5.07 (s, 1H), 5.70-5.83 (m, 1H), 6.84 (d, 1H), 6.92 (s, 1H) and 7.14 (d, 1H).
- C. The iminium salt **35** from above (26.8 mmol) was mixed with acetic acid (4 mL), dichloromethane (40 mL), methanol (80 mL) and water (40 mL) in a 250 mL round-bottom flask and stirred at room temperature for 18 h. The mixture separated into two phases and the organic phase was separated. The aqueous phase was extracted with dichloromethane. The organic extracts 25 were combined, washed twice with water and once with saturated aqueous sodium bicarbonate and dried over magnesium sulfate. The solvents were evaporated *in vacuo* to give 3,4-dihydro-6-methoxy-1-(1-propene-3-yl)-2(1H)-naphthalenone **36** as an oil, a single component by HPLC (>95%), 2.5 g (46% from **2**). ¹H NMR (CDCl₃): δ 2.52-2.70 (m, 4H), 2.92-3.15 (m, 2H), 3.45 (t, 1H), 3.81 (s, 3H), 4.97 (s, 1H), 5.03 (d, 1H), 5.65-5.81 (m, 1H), 6.74-6.82 (m, 2H) 30 and 7.08 (d, 1H).

D. A solution of crude naphthalenone 36 (2.5 g, 11.6 mmol) in methanol (50 mL) was treated with ammonium acetate (13.4 g, 0.173 mol) in a 100 mL round-bottom flask and stirred at room temperature for 10 min. Sodium cyanoborohydride (3.58 g, 57 mmol) was added and the resultant solution was heated at reflux for 3 h. The solvent was evaporated *in vacuo*, and the residue was treated with aqueous sodium hydroxide (50 mL of a 1N solution). The product was extracted into dichloromethane (2 x 50 mL). The organic extracts were combined, washed with water and dried over sodium sulfate. The solvent was evaporated *in vacuo*, and the residue was dissolved in diethyl ether (50 mL) and methanol (1-2 mL). The resultant solution was treated with ethereal hydrochloric acid (14 mL of a 1 N solution) to produce a gummy solid that coated the sides of the flask. The solvent was decanted and an additional 50 mL of ether was added, at which point the residue solidified. The product was collected by filtration, washed with diethyl ether and dried *in vacuo* to give *cis*-1,2,3,4-tetrahydro-6-methoxy-1-(1-propene-3-yl)-2-naphthalenamine hydrochloride 37a as a purple solid (1.75 g, a mixture of 2 components ~3:1 by HPLC). MS m/e (MH⁺) 218.

E. A solution of *trans*-4-[(benzenesulfonamido)methyl]cyclohexanecarboxylic acid (0.924 g, 3.31 mmol), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), (1.26 g, 3.31 mmol) and *N,N*-diisopropylethylamine (1.7 mL, 9.77 mmol) in *N,N*-dimethylformamide (10 mL) was stirred at room temperature in a 50 mL round-bottom flask for 15 min. Naphthalenamine hydrochloride 37a (0.80 g, 3.15 mmol) was added to the solution. Stirring was continued for an additional hour, and the resultant solution was poured into water (~100 mL). A gummy solid formed on the sides of the flask. Ethanol was added and the product crystallized upon heating. The mixture was cooled to room temperature and the product was collected by filtration and dried in *vacuo*, to give [1 α ,2 α (*trans*)]-4-[(benzenesulfonyl)amino]methyl]-N-[1,2,3,4-tetrahydro-6-methoxy-1-(1-propene-3-yl)-2-naphthalenyl]-cyclohexanecarboxamide 38 a light gray solid, 0.67 g (43 %), a single component by HPLC. MS (MH⁺) 497; ¹H NMR (CDCl₃):

δ 0.71-0.97 (m, 2H), 1.33-1.50 (m, 3H), 1.74-1.98 (m, 7H), 2.24-2.53 (m, 2H), 2.76-2.87 (m, 4H), 3.00-3.09 (m, 1H), 3.78 (s, 3H), 4.34-4.43 (m, 1H), 4.62 (t, H), 5.02 (s, 1H), 5.07 (d, 1H), 5.48 (d, 1H), 5.81-5.96 (m, H), 6.63 (s, 1H), 6.72 (d, 1H), 7.02 (d, 1H), 7.47-7.62 (m, 3H) and 7.84 (d, 2H).

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F. A solution of lithium aluminum hydride in tetrahydrofuran (4 mL of a 1.0 M solution, 4 mmol) was carefully added to a solution of carboxamide **38** (0.21 g, 0.422 mmol) in tetrahydrofuran (10 mL) in a 50 mL round-bottom flask. The resultant solution was heated at reflux for 24 h. The solution was cooled in a water bath, and the excess hydride was quenched by careful addition of water (0.16 mL) in tetrahydrofuran (5 mL) followed by 15% aqueous sodium hydroxide (0.16 mL) in tetrahydrofuran (5 mL) and finally water (0.5 mL). The inorganic solids were removed by filtration and washed generously with tetrahydrofuran. The filtrate was evaporated *in vacuo* and the resulting residue was dissolved in ethanol and treated with a saturated solution of hydrochloric acid in ethanol (2 mL). Evaporation and titration with diethyl ether afforded [1 α ,2 α (*trans*)]-N-[[[[1,2,3,4-tetrahydro-6-methoxy-1-(1-propene-3-yl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl]-benzenesulfonamide hydrochloride **39a** as a colorless solid, 0.118 g (54%), a single component by HPLC (>95 %). MS (MH⁺) 483; ¹H NMR (DMSO-d₆) δ 0.75-1.04 (m, 4H), 1.23-1.40 (m, 1H), 1.57-2.16 (m, 7H), 2.43-2.62 (m, 2H), 2.79-3.00 (m, 4H), 3.13-3.23 (m, 1H), 3.35-3.44 (m, 2H), 3.73 (s, 3H), 4.91 (d, 1H), 5.03 (d, 1H), 5.73-5.88 (m, 1H), 6.65-6.72 (m, 2H), 6.93 (d, 1H), 7.57-7.70 (m, 4H), 7.84 (d, 2H), 8.70 (br s, 1H, exchanges with D₂O), and 9.07 (br s, 1H, exchanges with D₂O).

25 (Figure 12).

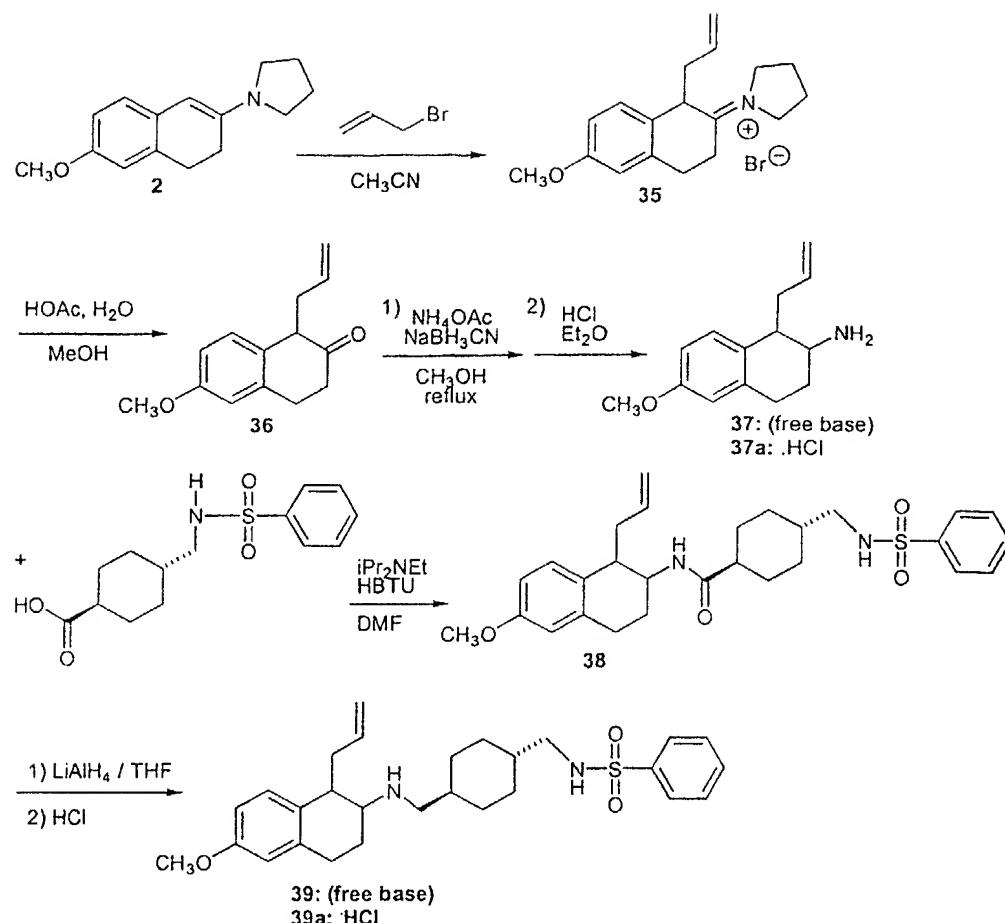


Figure 12

EXAMPLE 7

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rac-[1 α ,2 α (*trans*)]-*N*-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(3-hydroxypropyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] benzenesulfonamide (40)

10 A solution of borane (3.5 mL of a 1.0 M solution, 3.5 mmol) in tetrahydrofuran was added to a solution of carboxamide 38 (0.25 g, 0.503 mmol) in tetrahydrofuran (10 mL) in a 100 mL round-bottom flask. The resultant mixture was heated at reflux for 1 h. Water (1.5 mL) was carefully added and the mixture was heated at reflux for 1 h. Aqueous sodium hydroxide (50%, 0.5 mL) was added followed by hydrogen peroxide (30 %, 1.0

mL). The two phase system was stirred vigorously for 2 h. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The organic extracts were combined, dried over sodium sulfate, and the solvent was evaporated *in vacuo*. The residue was dissolved in ethanol and 5 treated with a saturated solution of hydrogen chloride in ethanol (2 mL). The solvent was evaporated and the residue was titrated with diethyl ether to give [1 α ,2 α (*trans*)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(3-hydroxypropyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] benzenesulfonamide hydrochloride 40 as a white solid 0.242 g (90%). The purity by HPLC is 80-10 90%. MS (MH $^+$) 501; 1 H NMR (DMSO-d₆) δ 0.75-0.97 (m, 4H), 1.02-1.13 (m, 1H), 1.16-1.51 (m, 5H), 1.58-2.18 (m, 8H), 2.54-2.63 (m, 2H), 2.73-3.12 (m, 4H), 3.28-3.46 (m, 3H), 3.72 (s, 3H), 6.64-6.73 (m, 2H), 6.97 (d, 1H), 7.54-7.69 (m, 4H), 7.80 (d, 2H), 8.57 (br s, 1H, exchanges with D₂O), and 8.93 (br s, 1H, exchanges with D₂O) (Figure 13).

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EXAMPLE 8

rac-[1 α ,2 α (*trans*)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(*n*-propyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] benzenesulfonamide
20 (42)

A. The carboxamide 38 (0.4 g, 0.805 mmol) was dissolved in methanol/dioxane (20 mL/20 mL) and hydrogenated (55 psi) over 10% palladium on carbon (catalytic) for 18 h. The catalyst was removed by filtration, 25 and the solvent was evaporated *in vacuo* to give [1 α ,2 α (*trans*)]-4-[(benzenesulfonyl)amino]methyl]-N-[1,2,3,4-tetrahydro-6-methoxy-1-(*n*-propyl)-2-naphthalenyl]-cyclohexanecarboxamide 41 as an off white solid (0.5 g, one component by HPLC). MS (MH $^+$) 499. 1 H (DMSO-d₆) δ 0.75-0.92 (m, 7H), 1.22-2.17 (m, 11H), 2.13 (m, 1H), 2.57 (t, 2H), 2.67-2.88 (m, 3H), 3.70 (s, 3H), 30 3.90-4.03 (m, 1H), 4.16 (d, 1H), 6.62-6.73 (m, 2H), 6.97 (d, 1H), 7.56-7.74 (m, 4H) and 7.80 (d, 2H); NMR also shows an unidentified impurity. This material was used without purification in the subsequent step.

B. A solution of borane in tetrahydrofuran (4.0 mL of a 1.0 M solution, 4.0 mmol) was added to a solution of the crude carboxamide 41 (0.43 g, 0.86 mmol) in tetrahydrofuran (10 mL). The resultant mixture was heated at reflux for 1 h. Water (1.5 mL) was slowly added to the cooled solution, which 5 resulted in considerable foaming. Concentrated aqueous hydrogen chloride (0.75 mL) was added and the solution was heated to reflux for 1 h. The solution was concentrated and the pH adjusted to 7-8 with aqueous sodium hydroxide (1N). The resultant solid was collected by filtration and washed with water. This material was dissolved in ethanol and treated with a saturated 10 solution of hydrogen chloride in ethanol. The hydrogen chloride salt of the product crystallized from the solution and was collected by filtration, washed with diethyl ether and dried *in vacuo* to give [1 α ,2 α (*trans*)]-*N*-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(*n*-propyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] benzenesulfonamide 42 as a colorless solid (0.147g, a 15 single component by HPLC). The mother liquors were evaporated, and the resultant residue titurated with diethyl ether to yield an additional 0.120 g of product. MS (MH⁺) 485; ¹H NMR (DMSO-d₆) δ 0.75-0.96 (m, 7H), 1.12-1.37 (m, 4H), 1.56-2.16 (m, 7H), 2.58 (t, 2H), 2.54-2.63 (m, 2H), 2.72-3.09 (m, 5H), 3.24-3.36 (m, 1H), 3.71 (s, 3H), 6.65-6.74 (m, 2H), 6.96 (d, 1H), 7.56-7.68 (m, 20 4H), 7.80 (d, 2H), 8.56 (br s, 1H, exchanges with D₂O), and 8.95 (br s, 1H, exchanges with D₂O) (Figure 13).

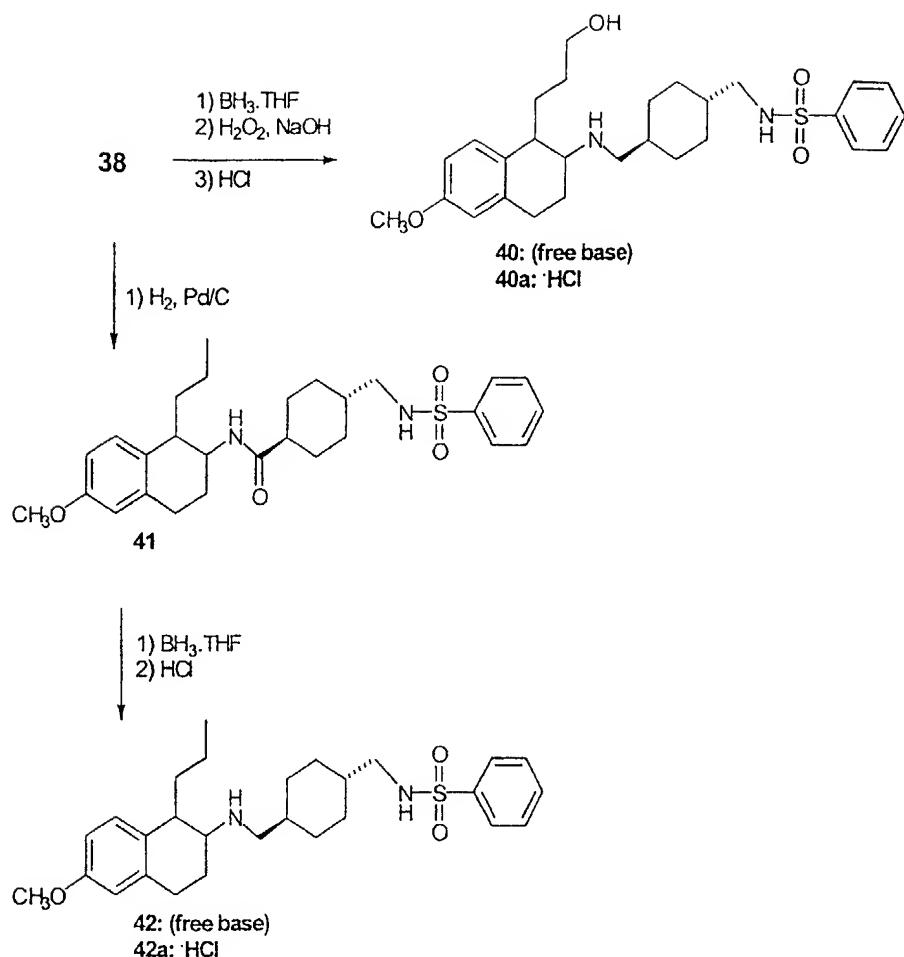


Figure 13

EXAMPLE 9

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*rac-[1 α ,2 α (*trans*)]-N-[[[[[1,2,3,4-tetrahydro-6-hydroxy-1-(3-pyridinylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] 2-fluorobenzenesulfonamide (44)*

10 The bis-amine salt of the starting material **43** (0.109 g, 0.174 mmol) was put into a 100 mL round-bottom flask along with 30 mL dichloromethane. To this stirred solution was added diisopropylethyl amine (0.067 mL, 0.385 mmol) which resulted in the dissolution of the starting material. This stirred solution was cooled on an ice bath. Boron tribromide in dichloromethane (1.74 mL of a 1 M solution, 1.74 mmol) was added to the amine solution and a precipitate

15

formed. This solution was stirred for about 2 hours while keeping on the ice bath at which time 4 mL methanol was added to quench the excess boron tribromide. The solvents were then removed *in vacuo* and the residue dissolved in 100 mL dichloromethane. The organic extract was washed twice
5 with 100 mL 0.02 M sodium hydroxide. An emulsion formed which was broken up by the addition of solid sodium chloride. The organic extract was washed once with 100 mL brine and then dried over magnesium sulfate followed by the removal of the solvents *in vacuo*. The residue was dissolved in methanol and ethanolic hydrogen chloride was added. The solvents were removed *in vacuo*
10 to give the crude product as a solid film. This material was further purified by heating briefly in isopropanol, allowing the solid to separate, followed by filtration, and then drying under vacuum to yield [1 α ,2 α (*trans*)]-*N*-[[[[1,2,3,4-tetrahydro-6-hydroxy-1-(3-pyridinylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] 2-fluorobenzenesulfonamide bis-hydrochloride 44 as a tan
15 powder (0.054 g, 0.088 mmol). MS (MH $^+$) 538; 1 H NMR (DMSO-d₆): δ 0.69-1.12 (m, 4H), 1.22-1.46 (m, 1H), 1.61-2.32 (m, 7H), 2.60-3.12 (m, 7H), 3.29-3.61 (m, 3H), 5.67 (d, 1H), 6.18 (dd, 1H), 6.52 (s, 1H), 7.30-7.51 (m, 2H), 7.63-7.84 (m, 2H), 7.85-8.02 (m, 2H), 8.27 (d, 1H), 8.62-8.84 (m, 2H), 9.03 (br, 1H), 9.45 (br, 1H) (Figure 14).

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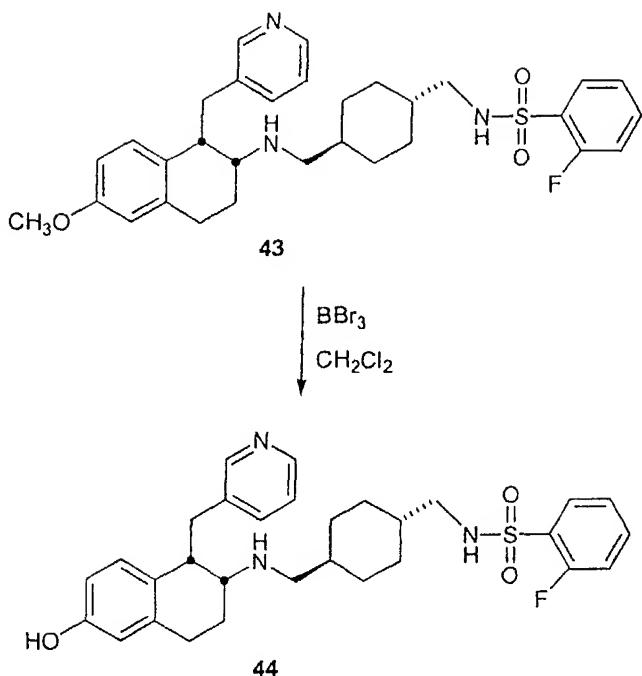


Figure 14

Other compounds of this invention having the formula 1 can be
 5 prepared using the methods described herein. There are over one thousand
 compounds that contain a phenylacetic acid moiety that are commercially
 available, and many more that are known, and these compounds can be
 converted to the corresponding β -tetralones using the chemistry described in
 EXAMPLE 4. These intermediates can be converted to products of formula 1
 10 that contain a wide variety of $(R_1)_n$ groups using the chemistry described in
 EXAMPLE 4. In some cases, the use of protecting groups may be needed and
 these manipulations are known to those skilled in the art. For example,
 aminophenylacetic acid can be converted to the corresponding phthalimide
 upon reaction with phthalic anhydride or N-carbethoxyphtalimide. Using the
 15 chemistry described in EXAMPLE 4A, phthalimido- β -tetralones can be
 prepared by substituting (phthalimido)phenyl acetic acids for 4-fluoroacetic
 acid, and these materials can be subsequently converted to products of
 formula 1 wherein, upon phthalimide cleavage, $(R_1)_n$ is amino (NH_2).
 Alkylamino (-NHR) and dialkylamino (-NR'R'') analogs can be prepared from
 20 the phthalimido- β -tetralone as well.

The use of alpha-substituted phenylacetic acid starting materials affords compounds of formula 1 wherein B_2 is alkyl or substituted alkyl and not hydrogen.

5

Compounds of this invention of formula 1 having a pyrimidyl, imidazolyl, thienyl or furyl substituent as R_2 can be prepared using the chemistry described in EXAMPLE 3 in which a β -tetralone is reacted with a heteroaryl aldehyde. For example furan- and thienyl-carboxaldehydes can be substituted 10 for 3-pyridylcarboxaldehyde in EXAMPLE 3A and reacted with β -tetralones and these intermediates can be subsequently converted to products of formula 1 wherein R_2 is 2-furyl or 3-furyl or 2-thienyl or 3-thienyl, and Y is methylene and m = 1. Similarly, N-trityl imidazole-carboxaldehyde can be used to produce 15 compounds of formula 1 in which R_2 is 2-imidazolyl or 4(5)-imidazolyl and Y is methylene and m = 1. Compounds of formula 1 in which the R_2 substituent is cyclopropyl and Y = methylene and m = 1 can be made using the chemistry described in EXAMPLE 1, substituting cyclopropylmethyl bromide for benzyl bromide. Compounds of formula 1 in which the R_2 substituent is phenoxy or 20 thiophenyl can be prepared by substituting chloromethylphenyl ether or a chloromethylphenyl sulfide for benzyl bromide in EXAMPLE 1.

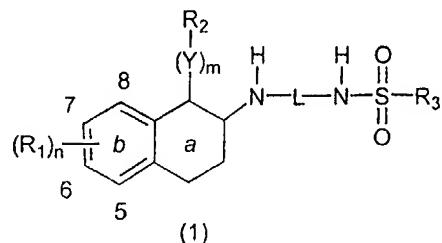
Compounds of formula 1 in which the R_2 substituent is piperidine can be made by reducing the corresponding pyridyl analog, such as that described in EXAMPLE 3, using catalytic hydrogenation conditions (i.e., platinum oxide on 25 carbon).

Compounds of formula 1 in which the R_3 substituent is heteroaryl can be prepared by substituting a pyridinyl, thienyl or furyl sulfonylchloride for 2-naphthylsulfonamide in EXAMPLE 3F. N-alkylimidazolylsulfonyl chlorides can 30 be used to prepare compounds of formula 1 in which the R_3 substituent is imidazolyl.

Additional compounds of this invention that were prepared using the experimental protocols described above include:

Mass Spectral Data of Compounds (1)

5



| # | R ₁ | R ₂ | Y=CH ₂ m= | L | R ₃ | Obs M ⁺ | Calc. Mass |
|----|----------------|----------------|-------------------------|--------------------------------------|--------------------------|-----------------------|---------------|
| 45 | (H) | Ph | 1 | (CH ₂) ₄ | 2-naphthyl | 499 | 498.7 |
| 46 | (H) | Ph | 1 | (CH ₂) ₅ | 2-naphthyl | 513 | 512.7 |
| 47 | 6-OMe | Ph | 1 | (CH ₂) ₇ | 2-naphthyl | 571 | 570.8 |
| 48 | 6-OMe | Ph | 1 | (CH ₂) ₈ | 2-naphthyl | 585 | 584.8 |
| 49 | 6-OMe | Ph | 1 | -H ₂ C--CH ₂ - | 2-naphthyl | 577 | 576.7 |
| 50 | 6-OMe | Ph | 1 | | 2-naphthyl | 555 | 554.7 |
| 51 | 6-OMe | Ph | 1 | -H ₂ C--CH ₂ - | 1-naphthyl | 583 | 582.8 |
| 52 | 6-OMe | Ph | 1 | -H ₂ C--CH ₂ - | Ph | 533 | 532.7 |
| 53 | 6-OMe | Ph | 1 | -H ₂ C--CH ₂ - | (3,4-diOMe)Ph | 593 | 592.8 |
| 54 | 6-OMe | Ph | 1 | -H ₂ C--CH ₂ - | (2-NO ₂)Ph | 578 | 577.7 |
| 55 | 6-OMe | Ph | 1 | -H ₂ C--CH ₂ - | (4-SO ₂ Me)Ph | 611 | 610.8 |
| 56 | 6-OMe | Ph | 1 | -H ₂ C--CH ₂ - | (3,5-diCl)Ph | 601 | 601.6 |
| 57 | 6-OMe | Ph | 1 | -H ₂ C--CH ₂ - | (2-F)Ph | 551 | 550.7 |
| 58 | 6-OMe | Ph | 1 | -H ₂ C--CH ₂ - | (4-F)Ph | 551 | 550.7 |
| 59 | 6-OMe | Ph | 1 | -H ₂ C--CH ₂ - | 2-thienyl | 539 | 538.8 |
| 60 | 6-OMe | Ph | 1 | -H ₂ C--CH ₂ - | (3-F)Ph | 551 | 550.7 |

| | | | | | | | |
|----|-------|------------|---|---------------------------------|--|-----|-------|
| 61 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2,4-diCl)Ph | 601 | 601.6 |
| 62 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (3-NO ₂)Ph | 578 | 577.7 |
| 63 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (4-NO ₂)Ph | 578 | 577.7 |
| 64 | 6-Cl | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-NO ₂)Ph | 582 | 582.1 |
| 65 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-CF ₃)Ph | 601 | 600.7 |
| 66 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-Cl)Ph | 567 | 567.1 |
| 67 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-CH ₂ NH ₂)Ph | 562 | 561.8 |
| 68 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-Br)Ph | 611 | 611.6 |
| 69 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (3-Br)Ph | 611 | 611.6 |
| 70 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (4-Br)Ph | 611 | 611.6 |
| 71 | 6-OH | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 519 | 518.7 |
| 72 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-NO ₂)Ph | 566 | 565.7 |
| 73 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-Cl)Ph | 555 | 555.1 |
| 74 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-Br)Ph | 599 | 599.6 |
| 75 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2,3-diCl)Ph | 589 | 589.6 |
| 76 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2,4-diCl)Ph | 589 | 589.6 |
| 77 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2,6-diCl)Ph | 589 | 589.6 |
| 78 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (3,4-diCl)Ph | 589 | 589.6 |
| 79 | 7-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 533 | 532.7 |
| 80 | 7-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | 2-naphthyl | 583 | 582.8 |
| 81 | 6-OMe | 2-naphthyl | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 583 | 582.8 |

| | | | | | | | |
|-----|-------|------------------------|---|---|------------------------|-----|-------|
| | | | | | | | |
| 82 | 6-OMe | 2-naphthyl | 1 | -H ₂ C-  -CH ₂ - | 2-naphthyl | 633 | 632.9 |
| 83 | 6-OMe | (3-OMe)Ph | 1 | -H ₂ C-  -CH ₂ - | Ph | 563 | 562.8 |
| 84 | 6-OMe | (3-OMe)Ph | 1 | -H ₂ C-  -CH ₂ - | 2-naphthyl | 613 | 612.8 |
| 85 | 6-OMe | (2-OMe)Ph | 1 | -H ₂ C-  -CH ₂ - | Ph | 563 | 562.8 |
| 86 | 6-OMe | (4-OMe)Ph | 1 | -H ₂ C-  -CH ₂ - | Ph | 563 | 562.8 |
| 87 | 6-OMe | (4-NO ₂)Ph | 1 | -H ₂ C-  -CH ₂ - | Ph | 578 | 577.7 |
| 88 | 6-OMe | (4-NO ₂)Ph | 1 | -H ₂ C-  -CH ₂ - | (2-NO ₂)Ph | 623 | 622.7 |
| 89 | 6-OMe | (2,6-diF)Ph | 1 | -H ₂ C-  -CH ₂ - | Ph | 570 | 568.7 |
| 90 | 6-OMe | (2,6-diF)Ph | 1 | -H ₂ C-  -CH ₂ - | (2-NO ₂)Ph | 614 | 613.7 |
| 91 | 6-OMe | (2-OMe)Ph | 1 | -H ₂ C-  -CH ₂ - | (2-NO ₂)Ph | 608 | 607.7 |
| 92 | 6-F | 3-pyridyl | 1 | -H ₂ C-  -CH ₂ - | (2-Cl)Ph | 556 | 556.1 |
| 93 | 6-OMe | (3-Cl)Ph | 1 | -H ₂ C-  -CH ₂ - | 2-naphthyl | 617 | 617.2 |
| 94 | 6-OMe | (3CF ₃)Ph | 1 | -H ₂ C-  -CH ₂ - | 2-naphthyl | 651 | 650.8 |
| 95 | 6-OMe | (2-Cl)Ph | 1 | -H ₂ C-  -CH ₂ - | Ph | 567 | 567.2 |
| 96 | 6-OMe | (3-Cl)Ph | 1 | -H ₂ C-  -CH ₂ - | Ph | 567 | 567.2 |
| 97 | 6-OMe | (4-Cl)Ph | 1 | -H ₂ C-  -CH ₂ - | Ph | 567 | 567.2 |
| 98 | 6-OMe | (2-CF ₃)Ph | 1 | -H ₂ C-  -CH ₂ - | Ph | 601 | 600.7 |
| 99 | 6-OMe | (3-CF ₃)Ph | 1 | -H ₂ C-  -CH ₂ - | Ph | 601 | 600.7 |
| 100 | 6-OMe | (4-CF ₃)Ph | 1 | -H ₂ C-  -CH ₂ - | Ph | 601 | 600.7 |
| 101 | 6-Br | Ph | 1 | -H ₂ C-  -CH ₂ - | Ph | 581 | 581.6 |

| | | | | | | | |
|-----|--------------------|--------------------|---|---------------------------------|---------|-----|-------|
| 102 | 6-Cl | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 537 | 537.1 |
| 103 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 521 | 520.7 |
| 104 | 7-Cl | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 537 | 537.1 |
| 105 | 5-Cl | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 537 | 537.1 |
| 106 | 8-Cl | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 537 | 537.1 |
| 107 | 6,7-F ₂ | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 539 | 538.7 |
| 108 | 6,7-diOMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 563 | 562.8 |
| 109 | 6,7-diOH | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 535 | 534.7 |
| 110 | 6-OH | CH=CH ₂ | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 469 | 468.6 |
| 111 | 6-F | 3-pyridyl | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-F)Ph | 540 | 539.7 |
| 112 | (H) | 3-pyridyl | 1 | <chem>-H2C-c1ccccc1{}</chem> | Ph | 490 | 489. |

5

IN VITRO ASSAYS

NPY5 HTS Centrifugation Assay

10

The compounds described in this invention were evaluated for binding to the human neuropeptide Y5 receptor.

Stable Transfection

15

- The human NPY5 receptor cDNA (Genbank Accession number U66275) was inserted into the vector pCIneo (Invitrogen) and transfected into human embryonic kidney cells (HEK-293) via Calcium phosphate method (Cullen 1987). Stably transfected cells were selected with G-418 (600 ug/mL).
- 5 Stably transfected cells served as the source for the membranes for the NPY5 receptor binding assay.

Membrane Preparation

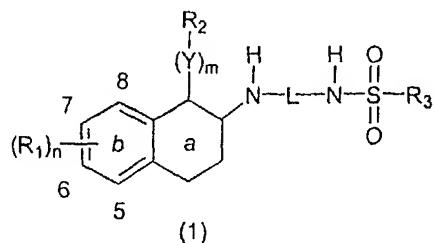
10 NPY5-transfected HEK293 cells were grown to confluence in 150 cm² culture dishes. Cells were washed once with phosphate-buffered saline (Gibco Cat# 14040-133). Cells were then incubated in phosphate-buffered saline without Calcium and without Magnesium, supplemented with 2 mM EDTA. Cells were incubated for 10 minutes at room temperature and the cells were
15 collected by repetitive pipeting. Cells were formed into pellets and then frozen at -80 until needed. Frozen pellets were homogenized with a polytron at full speed for 12 seconds in a homogenization buffer (20 mM Tris HCl, 5 mM EDTA, pH 7.4). Homogenates were centrifuged for 5 minutes at 4C at 200g. Supernatants were transferred to corex tubes and centrifuged for 25 minutes
20 at 28,000g. Pellets were re-suspended in Binding (20mM HEPES, 10 mM NaCl, 0.22 mM KH₂PO₄, 1.3mM CaCl₂, 0.8 mM MgSO₄, pH 7.4). Membranes were kept on ice until use.

25 A competition binding assay, known to those skilled in the art, was used in which aminotetralins (I) compete with ¹²⁵I-PYY for binding to cell membranes. In simple terms, the less ¹²⁵I-PYY bound to the membranes implies that a compound is a good inhibitor (competitor). Bound ¹²⁵I-PYY is determined by centrifugation of membranes, aspirating supernatant, washing away residual ¹²⁵I-PYY and subsequently counting the bound sample in a g-
30 counter.

Procedure for Radioligand binding assay

Compounds to be tested were prepared as 10x stocks in binding buffer and added first to assay tubes (RIA vials, Sarstedt). Twenty (20) μL of each 10x compound stock is pipeted into vials and 80 μL of ^{125}I -PYY (NEN catalog number NEX240), which has been diluted to a concentration of 200 pM in 0.25
5 % BSA in binding buffer, is added to the compound tubes (final concentration of ^{125}I -PYY is 80 pM). To each tube is added 100 μL of membranes and the mixture is agitated by pipeting 2 times. Samples are incubated for 1 hr at room temperature. Aluminum cast plates (Sarstedt) containing the vials are then centrifuged 10 minutes at 3200 rpm in a Sorvall RT6000. Supernatant is then
10 aspirated. To each vial 400 μL PBS is added and this is then aspirated again. Vials are then put in carrier polypropylene 12x75 tube and counted in gamma counter (Packard). Non-specific binding is determined in the presence of 300 nM NPY. Percent inhibition of ^{125}I -PYY binding is calculated by subtracting non-specific binding from the test samples (compound (I)), taking these counts
15 and dividing by total binding, and multiplying by 100. Inhibitory concentration values (IC_{50}) of compounds that show appreciable inhibition of ^{125}I -PYY binding are calculated by obtaining percent inhibition of ^{125}I -PYY binding values at different concentrations of the test compound, and using a graphing program such as GraphPad Prism (San Diego, CA) to calculate the concentration of test
20 compound that inhibits fifty-percent of ^{125}I -PYY binding (Table 4). These operations are known to those skilled in the art.

Binding Affinities of Compounds (1) for the Human NPY Y5 Receptor
 (expressed as % Inhibition of ^{125}I -PYY Binding)



5

| # | R ₁ | R ₂ | Y=CH ₂ m= | L | R ₃ | %Inh @ 3 uM |
|----|----------------|--------------------|-------------------------|---|--------------------------|----------------|
| 10 | 6-OMe | Ph | 1 | -H ₂ C-  -CH ₂ - | 2-naphthyl | 96 |
| 11 | 6-OMe | Ph | 1 | (CH ₂) ₅ | 2-naphthyl | 95 |
| 18 | 6-OMe | 3-pyridyl | 1 | -H ₂ C-  -CH ₂ - | 2-naphthyl | 96 |
| 26 | 6-F | Ph | 1 | -H ₂ C-  -CH ₂ - | (2-F)Ph | 107 |
| 34 | 6-OMe | Ph | 0 | -H ₂ C-  -CH ₂ - | 2-naphthyl | 46 |
| 39 | 6-OMe | CH=CH ₂ | 1 | -H ₂ C-  -CH ₂ - | Ph | 102 |
| 40 | 6-OMe | OH | 3 | -H ₂ C-  -CH ₂ - | Ph | 91 |
| 42 | 6-OMe | Me | 2 | -H ₂ C-  -CH ₂ - | Ph | 101 |
| 43 | 6-OMe | 3-pyridyl | 1 | -H ₂ C-  -CH ₂ - | (2-F)Ph | 100 |
| 44 | 6-OH | 3-pyridyl | 1 | -H ₂ C-  -CH ₂ - | (2-F)Ph | 101 |
| 45 | (H) | Ph | 1 | (CH ₂) ₄ | 2-naphthyl | 58 |
| 46 | (H) | Ph | 1 | (CH ₂) ₅ | 2-naphthyl | 89 |
| 47 | 6-OMe | Ph | 1 | (CH ₂) ₇ | 2-naphthyl | 79 |
| 48 | 6-OMe | Ph | 1 | (CH ₂) ₈ | 2-naphthyl | 68 |
| 49 | 6-OMe | Ph | 1 | -H ₂ C-  -CH ₂ - | 2-naphthyl | 60 |
| 50 | 6-OMe | Ph | 1 |  | 2-naphthyl | 44 |
| 51 | 6-OMe | Ph | 1 | -H ₂ C-  -CH ₂ - | 1-naphthyl | 95 |
| 52 | 6-OMe | Ph | 1 | -H ₂ C-  -CH ₂ - | Ph | 99 |
| 53 | 6-OMe | Ph | 1 | -H ₂ C-  -CH ₂ - | (3,4-diOMe)Ph | 100 |
| 54 | 6-OMe | Ph | 1 | -H ₂ C-  -CH ₂ - | (2-NO ₂)Ph | 94 |
| 55 | 6-OMe | Ph | 1 | -H ₂ C-  -CH ₂ - | (4-SO ₂ Me)Ph | 90 |
| 56 | 6-OMe | Ph | 1 | -H ₂ C-  -CH ₂ - | (3,5-diCl)Ph | 73 |
| 57 | 6-OMe | Ph | 1 | -H ₂ C-  -CH ₂ - | (2-F)Ph | 98 |
| 58 | 6-OMe | Ph | 1 | -H ₂ C-  -CH ₂ - | (4-F)Ph | 91 |
| 59 | 6-OMe | Ph | 1 | -H ₂ C-  -CH ₂ - | 2-thienyl | 102 |

| | | | | | | |
|----|-------|------------------------|---|---------------------------------|--|-----|
| 60 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (3-F)Ph | 94 |
| 61 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2,4-diCl)Ph | 94 |
| 62 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (3-NO ₂)Ph | 95 |
| 63 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (4-NO ₂)Ph | 93 |
| 64 | 6-Cl | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-NO ₂)Ph | 93 |
| 65 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-CF ₃)Ph | 0 |
| 66 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-Cl)Ph | 99 |
| 67 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-CH ₂ NH ₂)Ph | 91 |
| 68 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-Br)Ph | 100 |
| 69 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (3-Br)Ph | 93 |
| 70 | 6-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (4-Br)Ph | 95 |
| 71 | 6-OH | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 102 |
| 72 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-NO ₂)Ph | 106 |
| 73 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-Cl)Ph | 107 |
| 74 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-Br)Ph | 105 |
| 75 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2,3-diCl)Ph | 100 |
| 76 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2,4-diCl)Ph | 99 |
| 77 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2,6-diCl)Ph | 102 |
| 78 | 6-F | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (3,4-diCl)Ph | 92 |
| 79 | 7-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 93 |
| 80 | 7-OMe | Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | 2-naphthyl | 75 |
| 81 | 6-OMe | 2-naphthyl | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 89 |
| 82 | 6-OMe | 2-naphthyl | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | 2-naphthyl | 54 |
| 83 | 6-OMe | (3-OMe)Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 92 |
| 84 | 6-OMe | (3-OMe)Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | 2-naphthyl | 82 |
| 85 | 6-OMe | (2-OMe)Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 74 |
| 86 | 6-OMe | (4-OMe)Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 25 |
| 87 | 6-OMe | (4-NO ₂)Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 84 |
| 88 | 6-OMe | (4-NO ₂)Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-NO ₂)Ph | 85 |
| 89 | 6-OMe | (2,6-diF)Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | Ph | 98 |
| 90 | 6-OMe | (2,6-diF)Ph | 1 | <chem>-H2C-c1ccccc1"CH2-</chem> | (2-NO ₂)Ph | 97 |

| | | | | | | |
|-----|-----------|------------------------|---|-----------------------------------|------------------------|-----|
| 91 | 6-OMe | (2-OMe)Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | (2-NO ₂)Ph | 92 |
| 92 | 6-F | 3-pyridyl | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | (2-Cl)Ph | 100 |
| 93 | 6-OMe | (3-Cl)Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | 2-naphthyl | 60 |
| 94 | 6-OMe | (3CF ₃)Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | 2-naphthyl | 45 |
| 95 | 6-OMe | (2-Cl)Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 84 |
| 96 | 6-OMe | (3-Cl)Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 100 |
| 97 | 6-OMe | (4-Cl)Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 90 |
| 98 | 6-OMe | (2-CF ₃)Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 30 |
| 99 | 6-OMe | (3-CF ₃)Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 99 |
| 100 | 6-OMe | (4-CF ₃)Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 93 |
| 101 | 6-Br | Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 100 |
| 102 | 6-Cl | Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 100 |
| 103 | 6-F | Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 98 |
| 104 | 7-Cl | Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 97 |
| 105 | 5-Cl | Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 98 |
| 106 | 8-Cl | Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 104 |
| 107 | 6,7-diF | Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 103 |
| 108 | 6,7-diOMe | Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 99 |
| 109 | 6,7-diOH | Ph | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 101 |
| 110 | 6-OMe | CH=CH ₂ | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | Ph | 100 |
| 111 | 6-F | 3-pyridyl | 1 | <chem>-H2C(c1ccccc1)[CH2-]</chem> | (2-F)Ph | 100 |
| 112 | (H) | 3-pyridyl | 1 | <chem>-H2C(c1ccccc1){}</chem> | Ph | 95 |

Table 4

IN VIVO ASSAYS

5

Rodent Feeding Model:
Measurement of Food Intake in Food-Deprived Rats

Male Long-Evans rats (180-200 grams) are housed individually and are
10 maintained on a once-a-day feeding schedule (i.e. 10 a.m. until 4 p.m.) for five

days following quarantine to allow the animals to acclimate to feeding on powdered chow (#5002 PMI Certified Rodent Meal) during the allotted time. The chow is made available in an open jar, anchored in the cage by a wire, with a metal follower covering the food to minimize spillage. Water is available 5 ad-libitum.

Animals are fasted for 18 hours prior to testing. At the end of the fasting period, animals are administered either compounds of the invention or vehicle. Vehicle and test compounds are administered either orally (5 mL/kg) 60 10 minutes prior to the experiment, or 30 minutes prior when given subcutaneously (1 mL/kg) or intraperitoneally (1 mL/kg). Compounds of the invention are administered orally as a suspension in aqueous 0.5% methylcellulose-0.4% Tween 80, or intraperitoneally as a solution or suspension in PEG 200; compound concentrations typically range from 1 15 mg/kg to 100 mg/kg, preferably from 10-30 mg/kg. Food intake is measured at 2, 4, and 6 hours after administration by weighing the special jar containing the food before the experiment and at the specified times. Upon completion of the experiment, all animals are given a one-week washout period before retesting.

Percent reduction of food consumption is calculated subtracting the grams of food consumed by the treated group from the grams of food consumed by the control group divided by the grams of food consumed by the control group, multiplied by 100.

$$25 \quad \% \text{ change} = \frac{\text{Treatment} - \text{Vehicle}}{\text{Vehicle}} \times 100$$

A negative value indicates a reduction in food consumption and a positive value indicates an increase in food consumption.
30

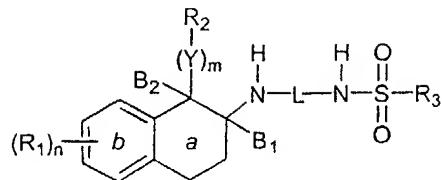
| Compound | Dose (mg/kg) (#rats) | Food Consumption (grams) | | |
|----------------------------|-------------------------|--------------------------|--------------------|--------------------|
| | | 0-2 hrs (%chg.) | 0-6 hrs (%chg.) | 2-6 hrs (%chg.) |
| 35 Vehicle PEG-2000 N=8 | | 8.63 g | 19.88 g | 11.25 g |

| | | | | | |
|----|------------------|------------------|--------------------|---------------------|--------------------|
| | 53 | 30 (i.p.) N=8 | 5.75 g (-33.3%) | 11.88 g (-40.2%) | 6.13 g (-45.6%) |
| 5 | Vehicle PEG-2000 | N=8 | 8.00 g | 18.5 g | 10.5 g |
| | 43 | 30 (i.p.) N=8 | 6.63 g (-17.1%) | 15.25 g (-17.6%) | 8.63 g (-17.8%) |
| 10 | 44 | 30 (i.p.) N=8 | 4.75 g (-40.6%) | 14.00 g (-24.3%) | 9.25 g (-11.9%) |
| | 111 | 30 (i.p.) N=8 | 5.13 g (-35.9%) | 12.63 g (-31.7%) | 7.50 g (-28.6%) |

15

What is claimed is:

1. A compound of formula 1



5 (1)

wherein

R₁ is independently selected from the group consisting of hydrogen; hydroxy; halo; C₁₋₈alkoxy; substituted C₁₋₈ alkoxy wherein the substituent 10 is halo; trifluoroalkyl; C₁₋₈alkylthio and substituted C₁₋₈alkylthio wherein the substituent is selected from halo, trifluoroalkyl and C₁₋₈alkoxy; C₃₋₆cycloalkyl; C₃₋₈cycloalkoxy; nitro; amino; C₁₋₆alkylamino; C₁₋₈dialkylamino; C₄₋₈cycloalkylamino; cyano; carboxy; C₁₋₅alkoxycarbonyl; C₁₋₅alkylcarbonyloxy; formyl; carbamoyl; phenyl; substituted phenyl 15 wherein the substituent is selected from halo, hydroxyl, nitro, amino and cyano;

n is 0-2

20 B₂ is selected from the group consisting of hydrogen; C₁₋₅alkyl; substituted C₁₋₅alkyl wherein the substituent is halogen;

Y is methylene

25 m 0-3

R₂ is selected from the group consisting of hydrogen; hydroxy; C₁₋₆alkyl; C₁₋₆alkenyl; C₃₋₇cycloalkyl; halo; phenyl; substituted phenyl wherein the substituent is selected from halo, C₁₋₆alkyl, C₁₋₆alkoxy, trifluoroC₁₋₆alkyl,

cyano, nitro, amino, C₁₋₆alkylamino, and C₁₋₆dialkylamino; naphthyl; phenoxy; substituted phenoxy wherein the substituent is selected from halo, C₁₋₆alkyl, C₁₋₆alkoxy, trifluoroC₁₋₆alkyl, cyano and nitro; phenylthio and substituted phenylthio wherein the substituent is selected from halo, 5 C₁₋₆alkyl, nitro and amino; a heteroaryl group such as pyridyl, pyrimidyl, furyl, thienyl, and imidazolyl; substituted heteroaryl wherein the substituent is selected from C₁₋₆alkyl and halo; and heterocycloalkyl;

B₁ is selected from the group consisting of hydrogen; C₁₋₅alkyl; substituted C₁₋₅alkyl wherein the substituent is halo; 10

L is selected from the group consisting of C₁₋₈alkylene; C₂₋₁₀alkenylene; C₂₋₁₀alkynylene; C₁₋₄alkylenecycloalkylC₁₋₄alkylene; C₂₋₄alkenylene cycloalkylC₂₋₄alkenylene; 15 C₂₋₄alkynylene cycloalkylC₂₋₄alkynylene; C₁₋₄alkylene arylC₁₋₄alkylene; and C₂₋₄alkenylene arylC₂₋₄alkenylene;

R₃ is selected from C₁₋₈alkyl; substituted C₁₋₈alkyl wherein the substituent is selected from alkoxy and halo; cycloalkyl; substituted cycloalkyl wherein the substituent is selected from alkoxy and halo; phenyl; substituted phenyl wherein the substituent is selected from C₁₋₈alkyl, halo, nitro, amino, alkylamino, alkylsulfonyl, alkoxy and cyano, naphthyl; substituted naphthyl wherein the substituent is selected from halo, nitro, amino and cyano; heteroaryl wherein the heteroaryl group is selected from pyridyl, pyrimidyl, furyl, thienyl and imidazolyl; and substituted heteroaryl wherein the substituent is selected from halo, nitro, amino and cyano; 20 25

and enantiomers, diastereomers, and pharmaceutically acceptable salts thereof. 30

2. A compound of claim 1 selected from the group consisting of:

rac-[1 α ,2 α (*trans*)]-N-[[[[1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] 2-naphthalenesulfonamide;

5

rac-[1 α ,2 α (*trans*)]-N-[[[[1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenyl]amino]methyl]-5-pentyl] 2-naphthalenesulfonamide;

rac-[1 α ,2 α (*trans*)]-N-[[[[1,2,3,4-tetrahydro-6-methoxy-1-(3-pyridinylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] 2-naphthalenesulfonamide; 2-

rac-[1 α ,2 α (*trans*)]-N-[[[[1,2,3,4-tetrahydro-6-fluoro-1-(phenylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] 2-fluorobenzenesulfonamide;

15

rac-[1 α ,2 α (*trans*)]-N-[[[[1,2,3,4-tetrahydro-6-fluoro-1-phenyl-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] 2-naphthalenesulfonamide;

rac-[1 α ,2 α (*trans*)]-N-[[[[1,2,3,4-tetrahydro-6-methoxy-1-(1-propene-3-yl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] benzenesulfonamide;

rac-[1 α ,2 α (*trans*)]-N-[[[[1,2,3,4-tetrahydro-6-methoxy-1-(3-hydroxypropyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] benzenesulfonamide; and

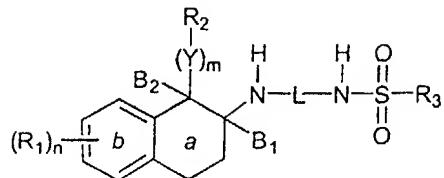
25

rac-[1 α ,2 α (*trans*)]-N-[[[[1,2,3,4-tetrahydro-6-methoxy-1-(*n*-propyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] benzenesulfonamide;

3. A compound of claim 1 wherein the salt is a hydrochloride salt.

30

4. A compound of claim 1 of the formula:



5 (1)

wherein

R₁ is independently selected from the group consisting of hydrogen; hydroxy; halo; C₁₋₈alkoxy; substituted C₁₋₈ alkoxy wherein the substituent is halo; trifluoroalkyl; C₁₋₈alkylthio and substituted C₁₋₈alkylthio wherein the substituent is selected from halo, such as chloro, bromo, fluoro and iodo, trifluoroalkyl and C₁₋₈alkoxy; C₃₋₆cycloalkyl; C₃₋₈cycloalkoxy; nitro; amino; C₁₋₆alkylamino; C₁₋₈dialkylamino; C₄₋₈cycloalkylamino; cyano; carboxy; C₁₋₅alkoxycarbonyl; C₁₋₅alkylcarbonyloxy; formyl; carbamoyl; phenyl; substituted phenyl wherein the substituent is selected from halo, hydroxyl, nitro, amino and cyano;

n is 0-2

20 B₂ hydrogen;

Y is methylene

m 0-3

25 R₂ is selected from the group consisting of hydrogen; hydroxy; C₁₋₆alkyl; C₁₋₆alkenyl; halo; C₃₋₇cycloalkyl; phenyl; substituted phenyl wherein the substituent is selected from halo, C₁₋₆alkyl, C₁₋₆alkoxy, trifluoroC₁₋₆alkyl, cyano, nitro, amino, C₁₋₆alkylamino and C₁₋₆dialkylamino; naphthyl;

phenoxy; substituted phenoxy wherein the substituent is selected from halo, C₁₋₆alkyl, C₁₋₆alkoxy, trifluoroC₁₋₆alkyl, cyano and nitro; phenylthio and substituted phenylthio wherein the substituent is selected from halo, C₁₋₆alkyl, nitro and amino; a heteroaryl group such as pyridyl, pyrimidyl, furyl, thienyl, and imidazolyl; substituted heteroaryl wherein the substituent is selected from C₁₋₆alkyl and halo; heterocycloalkyl;

- 5 B₁ is hydrogen;
- 10 L is selected from the group consisting of C₁₋₈alkylene; C₂₋₁₀alkenylene; C₂₋₁₀alkynylene;
C₁₋₄alkylenecycloalkylC₁₋₄alkylene; C₂₋₄alkenylenealcycloalkylC₂₋₄alkenylene;
C₂₋₄alkynylenealcycloalkylC₂₋₄alkynylene; C₁₋₄alkylenearylc₁₋₄alkylene; and
15 C₂₋₄alkylenearylc₂₋₄alkenylene;

- 20 R₃ is selected from C₁₋₈alkyl; substituted C₁₋₈alkyl wherein the substituent is selected from alkoxy and halo; cycloalkyl; substituted cycloalkyl wherein the substituent is selected from alkoxy and halo; phenyl; substituted phenyl wherein the substituent is selected from C₁₋₈alkyl, halo, nitro, amino, alkylamino, alkylsulfonyl, alkoxy and cyano; naphthyl; substituted naphthyl wherein the substituent is selected from halo, nitro, amino and cyano; heteroaryl wherein the heteroaryl group is selected from pyridyl, pyrimidyl, furyl, thienyl and imidazolyl; and substituted heteroaryl wherein the substituent is selected from halo, nitro, amino and cyano;
- 25 and enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

- 30 5. A compound of claim 1 wherein:

R₁ is hydrogen, alkoxy, nitro, halo, amino, hydroxy or alkylamino;

B₁ and B₂ are hydrogen;

m is 0-3;

5 n is 1-2;

R₂ is phenyl, substituted phenyl, naphthyl, heteroaryl, substituted heteroaryl or cycloalkyl;

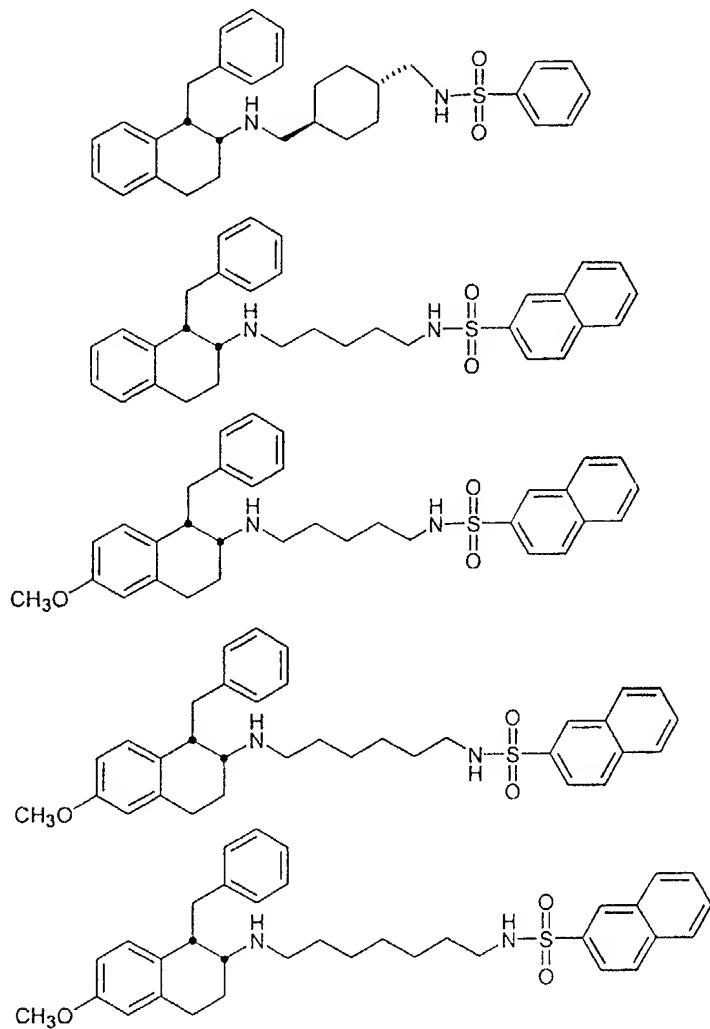
10 L = alkyl or alkylcycloalkyl;

R₃ is phenyl, substituted phenyl, naphthyl, or heteroaryl;

and the enantiomers, diastereomers and pharmaceutically acceptable
15 salts thereof.

6. The compound of claim 5 wherein the heteroaryl group is selected from the group consisting of pyridyl, furyl, thienyl and imidazolyl.

7. A compound of claim 1 selected from the group consisting of:

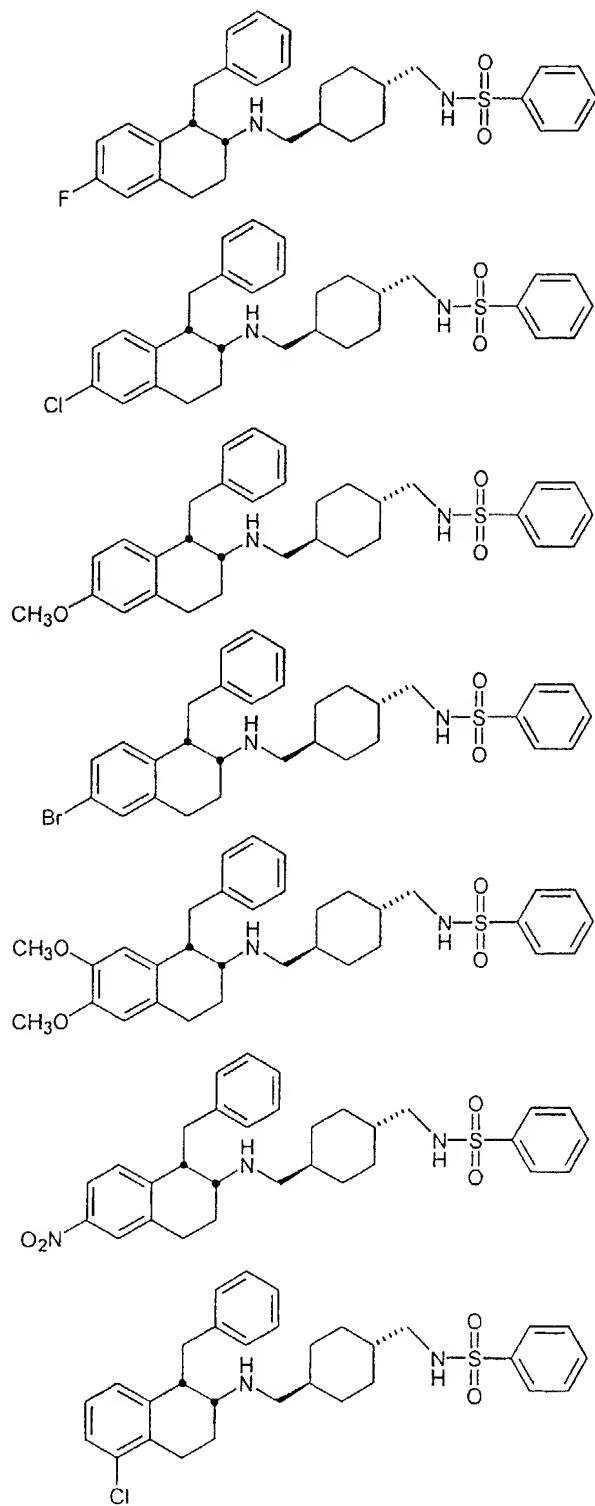


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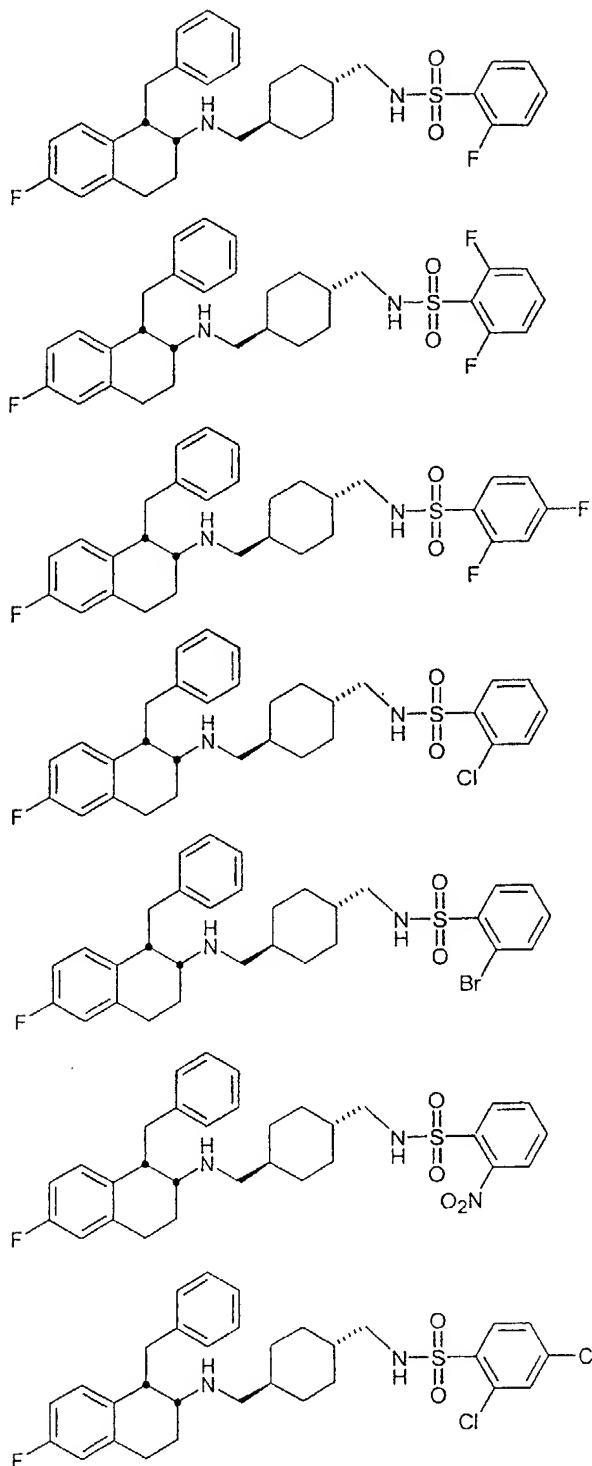
10

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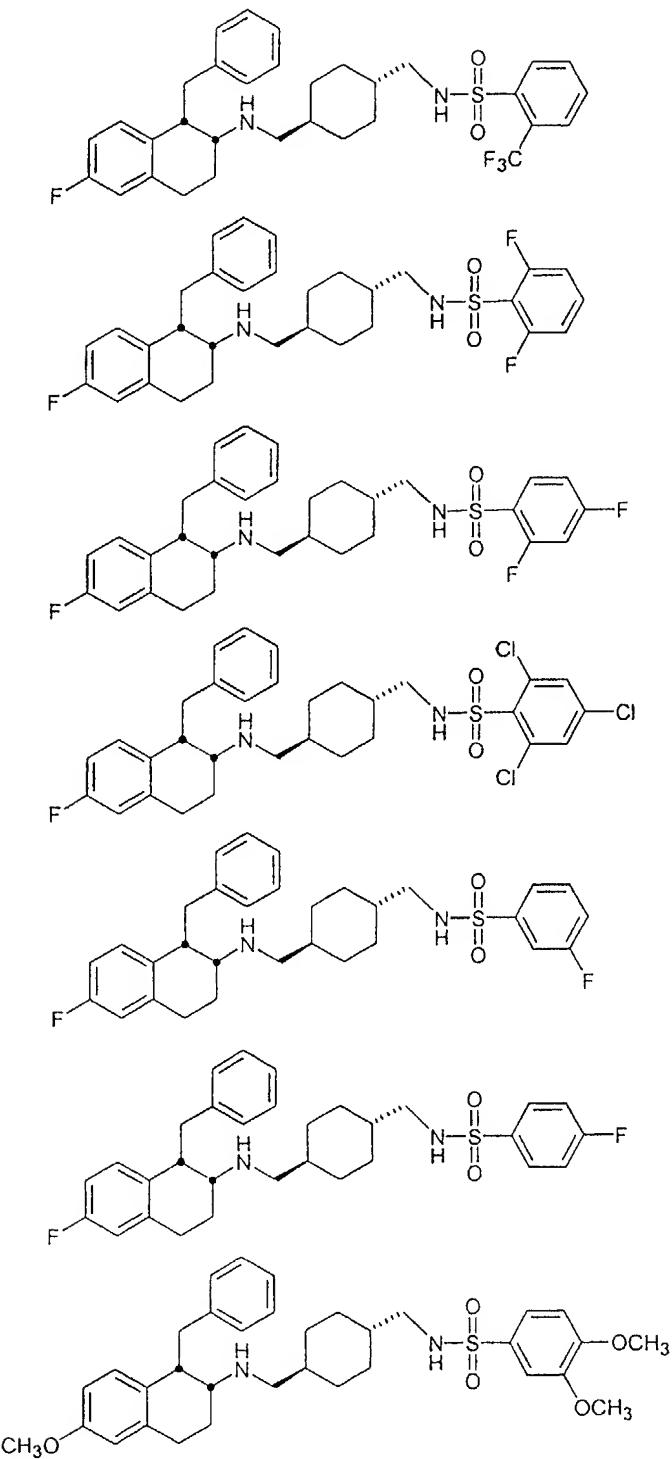
8. A compound of claim 1 selected from the group consisting of:



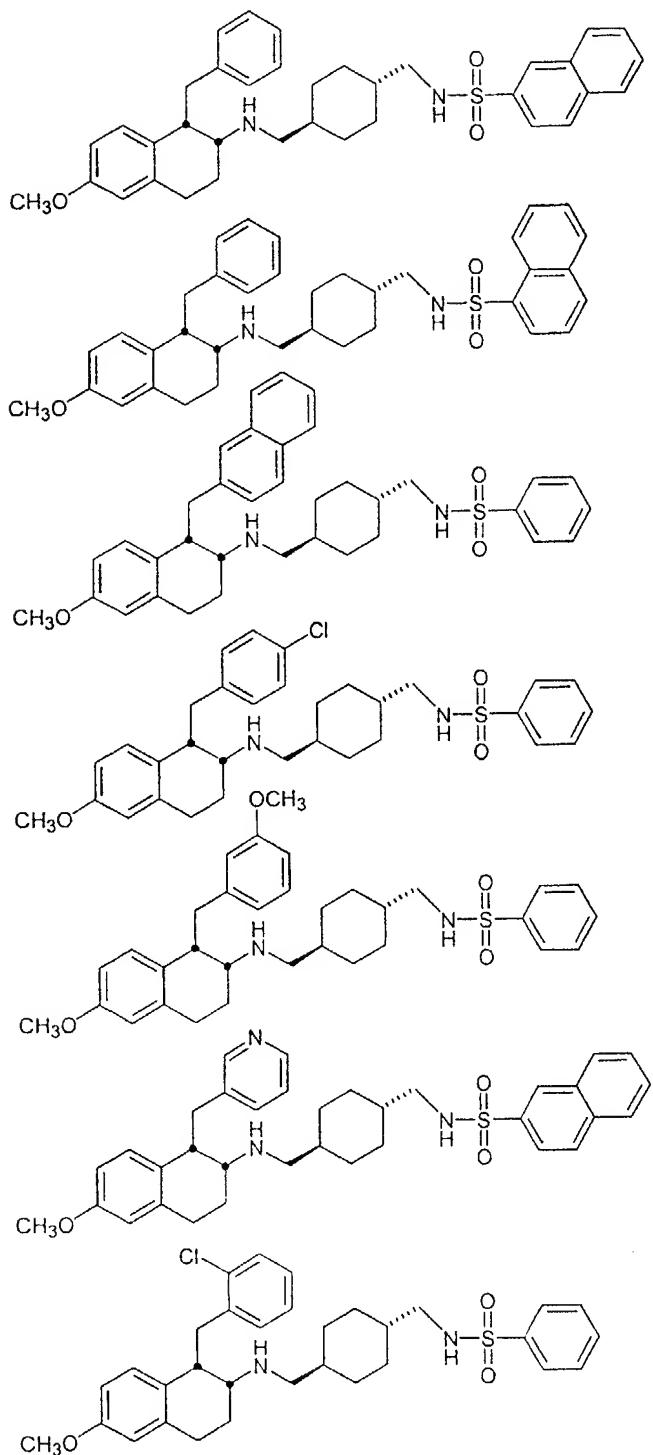
9. A compound of claim 1 selected from the group consisting of:



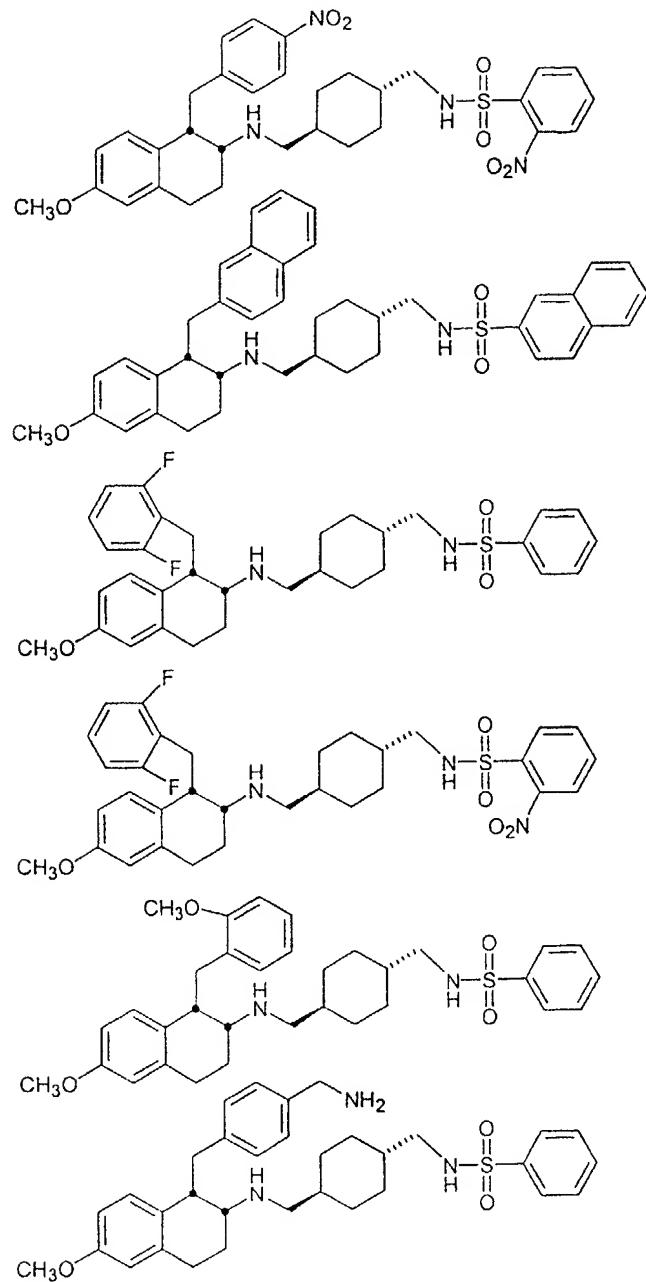
10. A compound of claim 1 selected from the group consisting of:



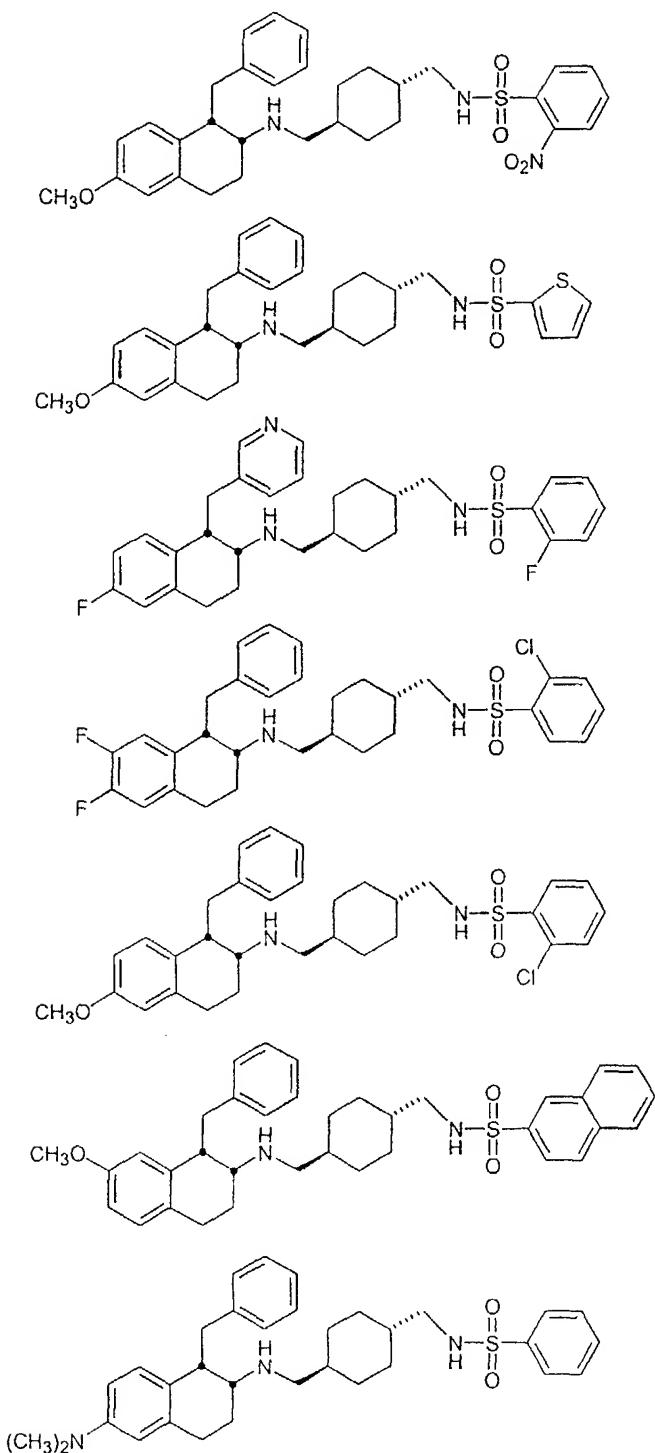
11. A compound of claim 1 selected from the group consisting of:



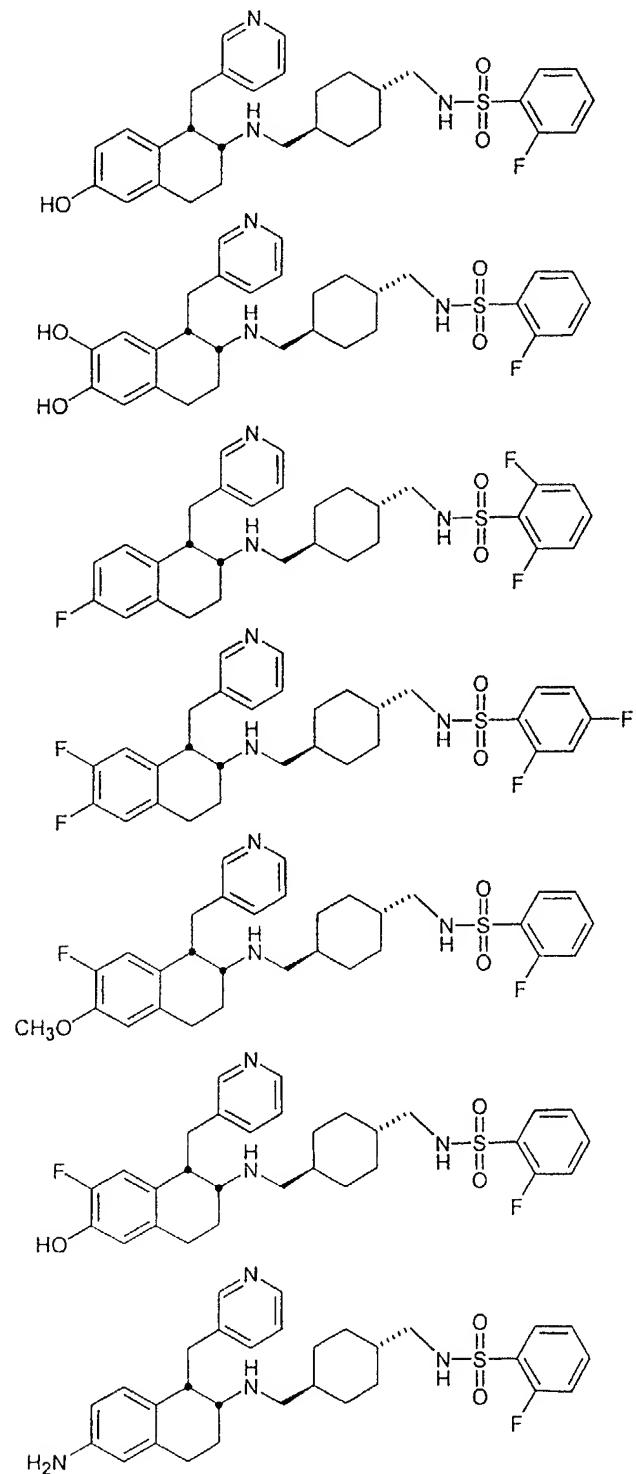
12. A compound of claim 1 selected from the group consisting of:



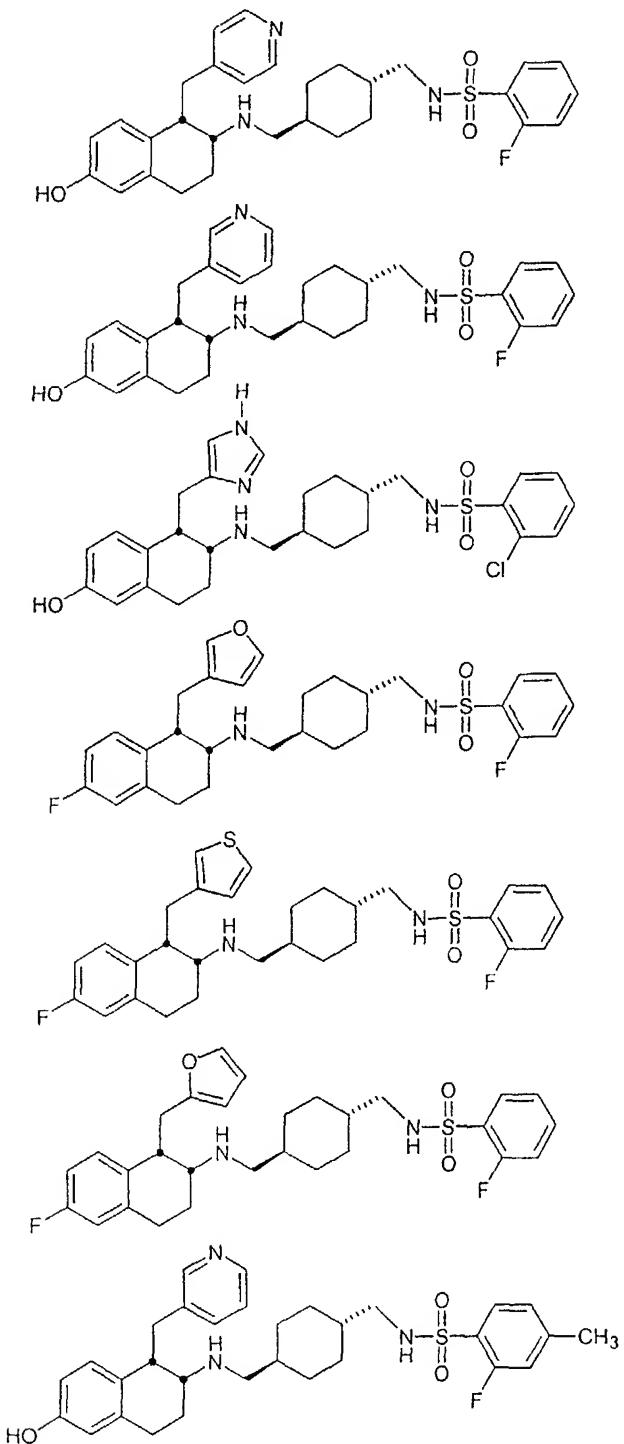
13. A compound of claim 1 selected from the group consisting of:



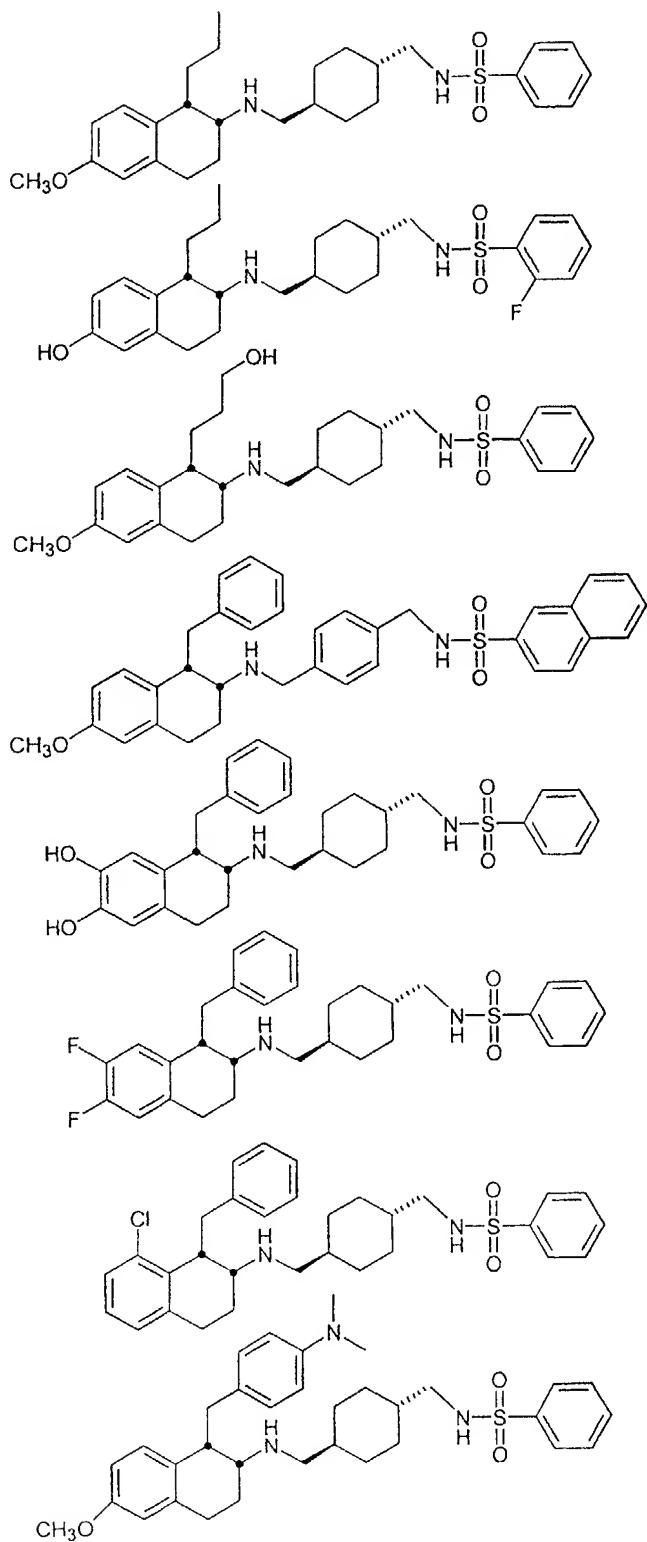
14. A compound of claim 1 selected from the group consisting of:



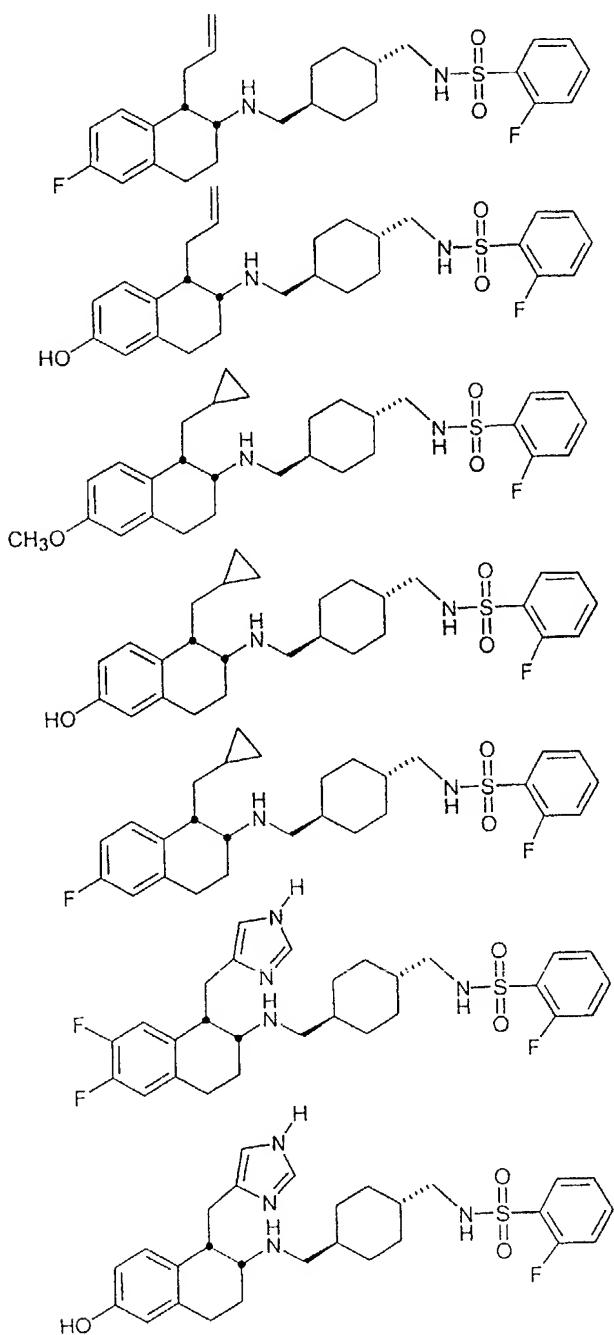
15. A compound of claim 1 selected from the group consisting of:



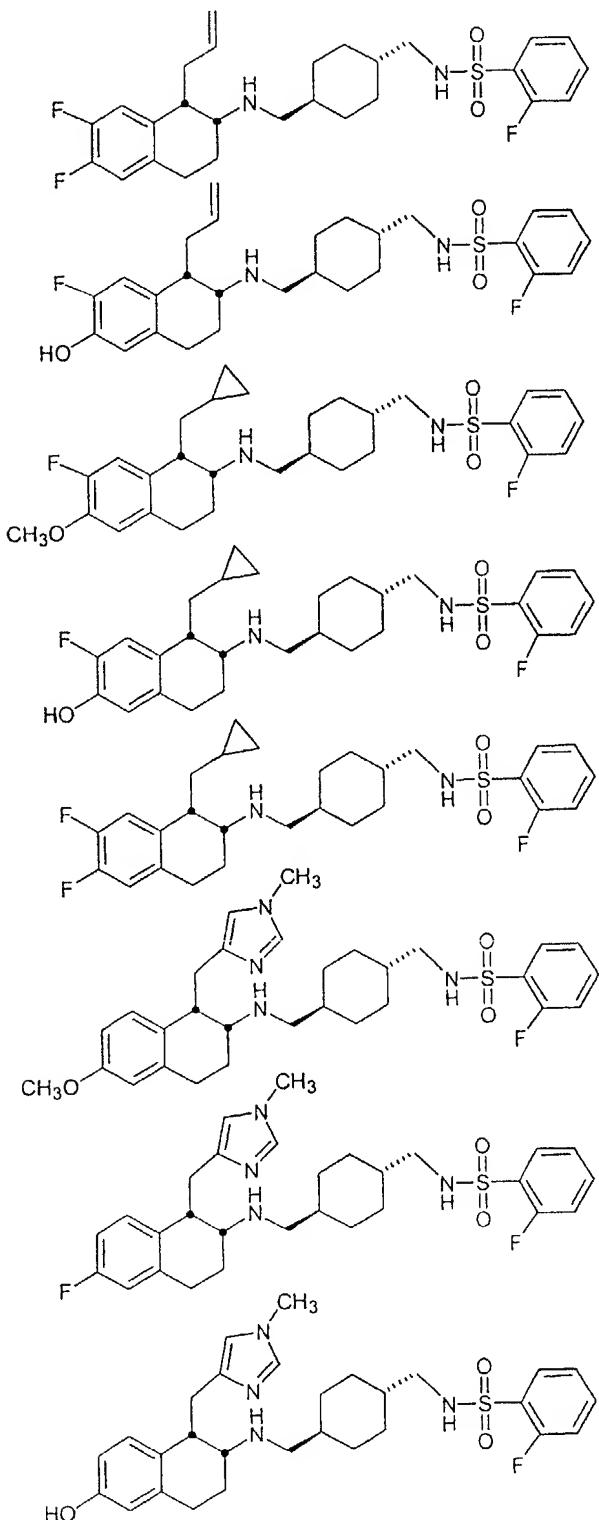
16. A compound of claim 1 selected from the group consisting of:



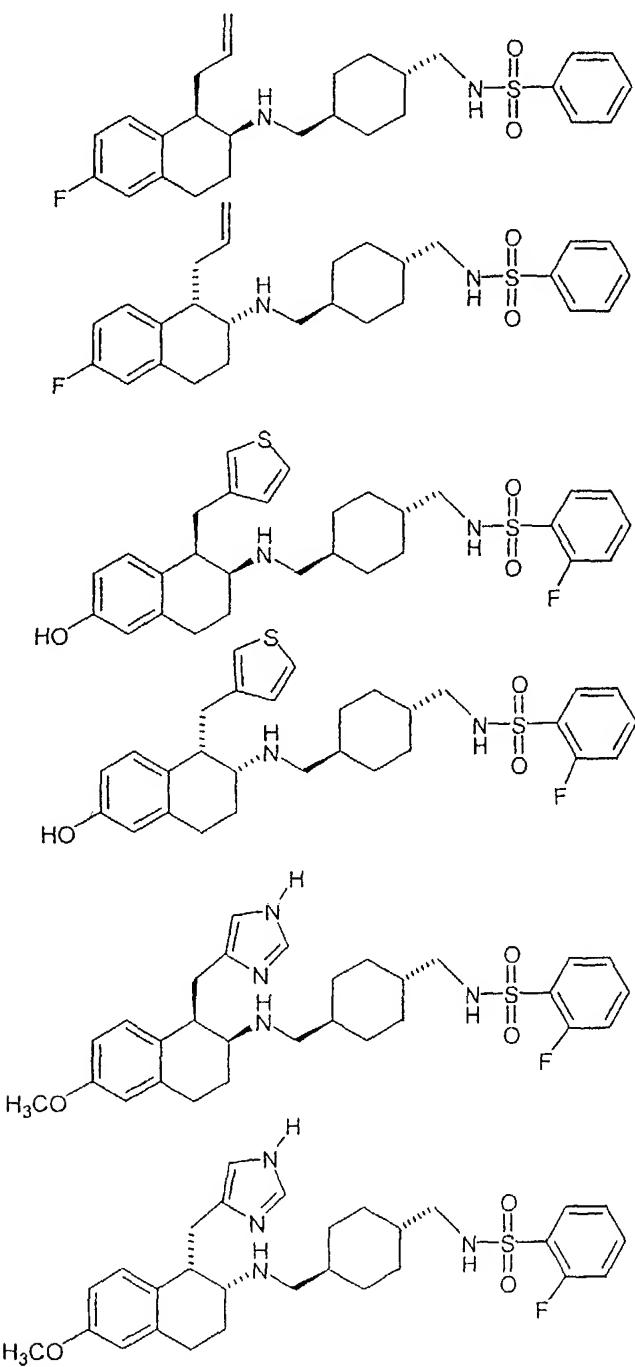
17. A compound of claim 1 selected from the group consisting of:



18. A compound of claim 1 selected from the group consisting of:



19: A compound selected from the group consisting of:



20. A method of treating disorders and diseases associated with NPY receptor subtype 5 comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 1.
- 5 21. A pharmaceutical composition for the treatment of diseases or disorders associated with the NPY Y5 receptor subtype comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.
- 10 22. A pharmaceutical composition according to claim 21 for the treatment of disorders or disease states caused by eating disorders, obesity, bulimia nervosa, diabetes, dyslipidimia, hypertension, memory loss, epileptic seizures, migraine, sleep disturbances, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure,
- 15 nasal congestion or diarrhea.

INTERNATIONAL SEARCH REPORT

Interr. Application No
PCT/US 99/07971

| A. CLASSIFICATION OF SUBJECT MATTER | | | | | |
|-------------------------------------|------------|------------|------------|------------|------------|
| IPC 6 | C07C311/15 | C07C311/20 | C07C311/21 | C07C311/37 | C07C311/25 |
| | C07D333/34 | C07D213/38 | C07D233/54 | C07D307/52 | C07D333/20 |
| | A61K31/18 | A61K31/44 | A61K31/34 | A61K31/38 | A61K31/415 |

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| A | EP 0 270 947 A (BAYER AG) 15 June 1988 (1988-06-15) page 73, line 33 – page 74, line 32; examples 45-54, 85, 109-115; claims 1-4, 9-15 --- | 1,22 |
| A | WO 97 20823 A (NOVARTIS AG) 12 June 1997 (1997-06-12) cited in the application claims --- | 1,20-22 |
| A | WO 97 19682 A (SYNAPTIC PHARMACEUTICAL CORP.) 5 June 1997 (1997-06-05) cited in the application claims ----- | 1,20-22 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

" Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| | |
|--|--|
| Date of the actual completion of the international search | Date of mailing of the international search report |
| 23 September 1999 | 05/10/1999 |
| Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016 | Authorized officer Van Amsterdam, L |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/07971

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 20
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 20
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/07971

| Patent document cited in search report | | Publication date | | Patent family member(s) | Publication date |
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| WO 9720823 | A | 12-06-1997 | | AU 7692996 A | 27-06-1997 |
| WO 9719682 | A | 05-06-1997 | | AU 1328197 A | 19-06-1997 |